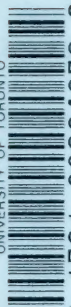


UNIVERSITY OF TORONTO



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GONORRHŒA

THE OXFORD MEDICAL PUBLICATIONS

GONORRHŒA

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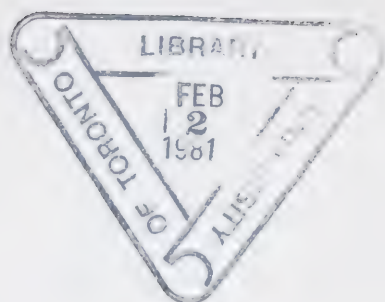
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TO MY TEACHER
SIR RONALD ROSS, K.C.B., K.C.M.G.
D.P.H., F.R.C.S., M.D., D.Sc., LL.D., F.R.S.
NOBEL LAUREATE

I DEDICATE THIS BOOK
IN MEMORY OF MANY YEARS OF RESEARCH UNDER HIS DIRECTION
AND
AS A TOKEN OF MY PROFOUND ADMIRATION FOR HIS GENIUS
SO WELL SPENT FOR THE BENEFIT OF HUMANITY

PREFACE

THIS book is dedicated to Sir Ronald Ross, because it is to a great extent a work of original research. I had the privilege to work under him for several years on tropical diseases, and I feel therefore that I owe much to his tuition in the art of investigation.

It has been my ambition to follow humbly his great example in an effort to do something, however little, to increase our knowledge of any disease which afflicts mankind.

It is the sincere hope, therefore, of my collaborators and myself that this book may mark a small advance in our knowledge and power over Gonorrhœa, which is an extraordinarily prevalent and serious venereal disease.

The first three years of the studies detailed in this work were carried out at the Military Hospital, Rochester Row, from 1916 to 1919, which was then under the command of Colonel L. W. Harrison, D.S.O., K.H.P. To him I owe a great debt of gratitude, since he aided and encouraged my investigations in a most sympathetic and tangible manner. His profound clinical and pathological knowledge of the subject was of great service in guiding me into the proper channels of research.

It was originally my intention to bring out a series of papers dealing with the bacteriology of the disease. After the first three years, however, so much data was accumulated from constant work, as well as from extensive investigations into the past literature, that it became necessary to bring all the information together into book form. During the next three years I had almost completed Parts I., II., III., and IV., which form essentially a compilation of research and reference.

These parts of the book should be of value to the up-to-date modern practitioner as well as to the bacteriologist and the venereal specialist. It is quite evident that bacteriology, serology, and immunity are rapidly becoming so advanced and important that, for the successful diagnosis and treatment of disease, a thorough knowledge of these subjects is required by the physician.

A great amount of time and care has been spent on the references, which reach a total of nearly two thousand. It is hoped that the numerous extracts gleaned from the literature of many countries, including America, France, Germany, etc., will give the reader a broad and unbiassed view of the whole subject.

In order to complete the work, Parts V. and VI. were added. Part V. comprises a chapter on prophylaxis by myself and a very full chapter on abortive treatment by Mr. C. H. Mills. Part VI. on the "Clinical Manifestations and the Practical Modern

"Treatment of Gonorrhoea," by Mr. David Lees, is a large and extremely important addition from the clinical point of view, and should be of great value to the general practitioner.

It is almost unnecessary to say that I am very much indebted to Mr. Lees, Mr. Mills, Dr. R. Thomson, and Dr. MacLachlan for their invaluable contributions.

I owe much to my esteemed colleagues, Dr. Allport and Mr. Mills, who placed all their knowledge at my disposal, and allowed me full scope in their clinics. It has been a great pleasure to me to be associated with them.

To my brother, Dr. Robert Thomson, I am extremely indebted, not only for his chapters on the Anatomy of the Genito-urinary Tract, but also for his constant assistance in correcting the proofs and in preparing the index, both of which have been very arduous tasks.

I was very lucky to have the skilled assistance of Mrs. Van Scherpenberg for the translation of foreign literature, and I wish here to express my great appreciation of her work.

With regard to the illustrations, all the microphotographs were taken by myself by means of a mercury vapour lamp apparatus. The coloured plate and ink sketches in Part I. were constructed by Colonel Harrison and myself for publication in the reports of the Medical Research Committee, and have been reproduced by the kind permission of the latter. The histological diagrams by Motz are reproduced by the courtesy of the publishers of the *Annales des maladies des organes génito-urinaires*.

I have much pleasure here in thanking the late laboratory staff at the Rochester Row Military Hospital. Through the strange happenings brought about by the Great War, men of marked ability drifted by fate into that laboratory. Thus I had the good fortune during my three years of research there to secure as my assistants Sergt. A. Denny (Science Master), Sergt. C. H. Holland, Private Frank Newbold (artist), and Mr. N. Clark. All of these men filled their temporary army posts with great distinction.

During the past three years my permanent assistants, Mr. E. S. Dean and Mr. F. T. M. Downing, have been constantly helping me with the researches detailed in this book. No man can do highly technical modern research without skilled assistants, and to these two men I owe a debt of gratitude. Most of the black-and-white drawings in this treatise were executed by Mr. Dean.

Finally, I must not omit to thank Staff-Sergeant Osborn and Miss Pike for the arduous task of typing the manuscript.

DAVID THOMSON.

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PART I

THE BACTERIOLOGY OF GONORRHOEA

CHAPTER I

HISTORICAL

CONFUSION WITH SYPHILIS—DISCOVERY OF THE GONOCOCCUS

EXACT data regarding the antiquity of gonorrhœa, its first appearance in the human race, and its mode of spread over the whole world, are unfortunately missing. It is proved beyond any doubt, however, that the disease was known to all the ancient civilised races, and reports on it are found in the Bible and in ancient medical works. The word gonorrhœa means flow of semen, and comes from the Greek γόνος (seed), and ῥέω (flow). Some believe that the word was invented by Hippocrates, and there is evidence that Hippocrates, in the fifth century before Christ, was cognisant of the disease, both in men and in women. It was also known to the ancients that gonorrhœa was infectious and carried by contact from one person to another. This contagious character was so generally recognised in the Middle Ages that attempts were made to prevent the spread of the disease by prophylactic measures, such as police regulations and the examination of prostitutes. This knowledge was unfortunately almost completely lost, when, towards the middle of the fifteenth century, syphilis made its appearance in Europe, and spread as an enormous epidemic over all the countries of the old world. At that time this new—or, at any rate, little prevalent and little known—venereal disease got such a hold on the interest of physicians and laymen that the other venereal diseases—gonorrhœa, balanitis, and soft sore—were soon not regarded as independent conditions. Eventually all were identified with syphilis, and gonorrhœa came to be regarded by some as a special form of syphilis, and by others as a mild variety of this disease. This teaching of the identity of gonorrhœa and syphilis obtained further support as the result of the unfortunate vaccination experiment of John Hunter (1786). He inoculated himself with the purulent matter from a syphilitic sore on the penis, and developed both syphilis and gonorrhœa. This added greatly to the confusion, until Ricord (1832) demonstrated by a series of comprehensive experiments that the two diseases were distinct, different and independent of each other. Fortunately his work was generally acknowledged. It is true that before Ricord's time, Balfour (1767), Bell (1793), Hernandez (1812), and others had tried to overthrow the identity theory, but their work did not apparently carry conviction, and it must be admitted that the general acknowledgement of the non-identity of these diseases was due to Ricord's brilliant dissertation. Langlebert (1864), Fournier (1869), Profeta, etc., adhered entirely to Ricord's view, and only a few authors, such as Diday (1867) and Zeissl (1902), opposed the dual theory. The latter held out in spite of overwhelming evidence, even up to the last decade of the nineteenth century.

Ricord, strange to say, although convinced of the contagious character of syphilis, was entirely opposed to the opinion that gonorrhœa was of an infectious nature. He

maintained that gonorrhœa was simply a catarrh of the urethral mucous membrane, caused by a diversity of irritants. He held that inoculation of the gonorrhœal pus produced catarrh by virtue of its irritating effect, and not by an organic virus. Moreover, he believed that menstrual, lochial, and puerperal discharges could cause gonorrhœa in man by their irritant property, in the same manner as the urethral injection of strong chemicals. In support of this view he referred to experiments whereby a purulent exudate was produced by the urethral injection of ordinary chemical irritants. He also referred to clinical observations, wherein he pointed out that a man often acquired the disease from a woman who had no true purulent discharge. In the first place he had overlooked the fact that urethral suppuration, due to chemical irritation, disappears spontaneously soon after the application of the irritant is discontinued; and secondly, he did not know that leucorrhœa was often merely a symptom of chronic gonorrhœa.

Fortunately Ricord's erroneous teaching regarding the non-contagious character of gonorrhœa was soon contradicted. During the next ten years it was shown that inoculation with minute traces of true gonorrhœal pus was regularly followed by an attack of the disease, whereas urethral inoculations with large quantities of other kinds of pus were without effect, and never produced any discharge.

When at last it had dawned on the medical profession that the disease was undoubtedly contagious, efforts were soon made to discover the virus, and many species of organisms were put forward as to the specific cause of the malady. Donn  (1844) discovered a kind of infusorian—" *Trichomonas* "; Thiry speaks of a " *Virus granulex* "; Jousseau (1862) described an " *Alga genitalis*," and both Salisbury and Hallier (1872) seemed to regard a kind of hyphomycete as the possible cause. The experiments and the results produced by these authors were so inconclusive, however, that they found no real acknowledgement even with their contemporaries.

The Discovery of the Gonococcus.—This uncertain groping in the dark was suddenly changed when Neisser (1879), recognising the importance of the bacteriological technique founded by Weigert and Robert Koch, commenced to investigate the gonorrhœal secretion by up-to-date methods, which resulted in the discovery of the gonococcus. In his first publication, *A New Species of Coccus Specific to Gonorrhœa* (1879), he confined his attention to the proof that the gonococcus was found regularly and was the principal organism in all fresh cases of gonorrhœa in men and women, and that similarly it was the chief organism in gonorrhœal conjunctivitis. He further described the shape and other characteristics of the new coccus. He based his observations on thirty-five cases of gonorrhœa in men, nine cases of acute vaginal discharge in females, and on two cases of purulent ophthalmia in adults and seven cases of gonorrhœal ophthalmia in infants. This new organism was described by Neisser as being a diplococcus, whose opposing sides were generally flattened out, giving a characteristic coffee-bean shape. He also pointed out the peculiar grouping of the germs within the pus cells and upon the epithelial cells, and further, that the free extracellular forms were usually found in groups of four, eight, twelve, etc., and never in chains.

He emphasised the regular occurrence of this germ in all cases of gonorrhœa and its absence in the pus of all other diseases, but stated that the final proof could only be obtained by isolating pure cultures, and by the successful production of the disease by inoculation with the pure germs.

In the following three years no new discoveries of any importance were added to Neisser's work. The majority of workers, Bokai (1880), Aufrecht, Weiss, Haab (1881), Hirschberg, Krause (1882), etc., were able to confirm Neisser's statements almost completely. Only a very few of the authors denied the existence of the gonococcus, and its regular and constant appearance in the gonorrhœal secretions. The reasons for their disbelief were due to the fact that they mistook the gonococcus for the ordinary pyogenic cocci, and also because the gonococci could be demonstrated in many old chronic vaginal and urethral discharges and in urethral shreds, which, according to the current and

widespread views of Noeggerath, were not considered to be true gonorrhœal conditions. On the other hand, many lochial discharges which had undoubtedly caused ophthalmia neonatorum were found to be apparently free from gonococci [Sattler and Schirmer (1882)]. The latter observation was especially a surprise, since, before Neisser's discovery, it was considered by clinicians that the irritating effects of lochial discharges of even healthy non-gonorrhœal mothers played a considerable part in the causation of ophthalmia neonatorum. Cedergold estimated that about one-third of the cases were due entirely to this irritation, and Credé believed that even more than one-half of them were purely irritative conditions.

Further, the inability to find the germs in the vulvo-vaginitis in little girls, which sometimes occurred in hospitals in epidemic form, led some to disbelieve in the ætiological importance of the gonococcus.

These erroneous and weakly founded observations were soon upset, however, by Zweifel (1884), Oppenheimer (1884), Kröner (1884), Welander (1884), Leopold and Wessel (1884), etc. These authors proved by a large number of exact and careful observations that all suppurations and secretions which contained gonococci were infectious, and that all complications such as gonorrhœal ophthalmia always came from an infection with gonorrhœal secretions. On the other hand, they showed that secretions such as lochial discharges in which no gonococci could be found by repeated painstaking examinations, proved always to be non-infectious when inoculated experimentally into the conjunctiva or urethra.

Neisser (1882), in a second paper, described the morphological characteristics of the gonococcus, its mode of division, and its characteristic appearance within the pus cells. He reported further upon certain cultivation experiments. He attempted to grow the organism on peptone gelatin, and on microscopic examination it appeared to him that growths had taken place. He stated, however, that the final proof that the germ was the cause of the disease was still lacking, as he had not inoculated these cultures into the human urethra. The final proof of the ætiological importance of the gonococcus was eventually established by culture and inoculation by Bumm (1885). He was the first to grow, with certainty, pure cultures of the gonococcus, on a medium composed of coagulated human blood serum. He established, moreover, beyond all doubt that the germ was the cause of the disease, by successfully producing gonorrhœa through inoculation of pure cultures into the male urethra.

With regard to all definitely proved and generally accepted scientific facts, one always finds an isolated sceptic with a marked or mild degree of misbelief. A little scepticism, however, is perhaps good at times, as it stimulates further experiment; too much, however, strangles progress.

Warden (1913) communicated a paper suggesting that many of the Gram-negative kidney-shaped cocci found in acute gonorrhœa were really a species of staphylococcus, and that any diagnosis made from the examination of microscopic smears was unreliable. He also suggested that gonorrhœa was really due to a double or symbiotic infection with gonococci and staphylococci.

Crabtree (1914), however, made a special investigation with regard to Warden's observations, and showed that "the evidence as presented by Warden that gonorrhœal urethritis is due to the staphylococcus albus is based on erroneous interpretations of his observations and is fallacious."

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CHAPTER II

THE MORPHOLOGY OF THE GONOCOCCUS

SHAPE AND SIZE—EXTRA- AND INTRACELLULAR CHARACTERISTICS

The Shape and Size of the Gonococcus.—In stained smears of gonorrhoeal pus, the gonococci are seen to lie in pairs. As a rule the individual cocci have a kidney or coffee-bean shape, and the flattened surfaces lie opposed to each other. Neisser described this characteristic appearance in his first treatise in 1879. Sometimes the cocci appear more or less round, but by far the greater number of them are hemispherical, with a distinct notch or indentation on their flattened side. According to Neisser, who studied their mode of division very carefully, the cocci are more or less spherical in their earliest stages. Soon, however, they lengthen and become ovoid, a constriction appears in the centre, and in this way diplococci are formed, which at first have the shape of the figure 8. Each half of the eight-form, however, soon lengthens out at right angles to the long axis of the eight, and the opposing sides become flattened. As the process proceeds the split between the cocci becomes more oval, and thereby a notch is produced in the flat surface of each coccus. This notch deepens and becomes the starting-point of a new line of fission, so that at the conclusion of the division phase, four cocci, or two pairs of diplococci, lie closely and compactly together.

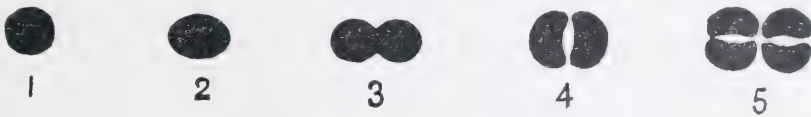


FIG. 1.

From each coccus, therefore, there is always eventually produced a tetrad, which lies in one plane, and so it comes about that they gradually spread over flat surfaces and never assume long chain forms like the streptococcus. It is very characteristic to find them plastered over the flat surfaces of the epithelial cells, in groups of four, eight, sixteen, etc.

The characteristic bean-shaped pairs are most commonly found within the pus cells, and, with the exception of the meningococcus, no other known cocci have these peculiar and distinctive features.

The fact that characteristic kidney-shaped forms are most commonly seen, as in No. 4, led Scholtz (1899) to infer that the other phases of division (1, 2, and 3) are much more rapid, and not so long drawn out as phase 4.

The size of the individual cocci, and of the pairs, must of course vary according to the stage of the development. The fully developed coffee-bean forms have, according to the measurements of Bumm, a length of 1.6μ from pole to pole, and a breadth of 0.8μ in their widest middle portion. He states that the very young forms of diplococci with only

slightly marked fission between them measure $0.8\ \mu$ long by $0.6\ \mu$ broad. The individual fully developed cocci of a pair form each $\frac{1}{10}$ ths of the mass, and the remaining $\frac{9}{10}$ ths is occupied by the fissure. It must be understood, however, that the process of fixing and staining produces some alteration in the size of organisms. Thus alcoholic fixation, more especially in smear preparations, causes a reduction in size, due to shrinking; also lightly stained cocci are somewhat smaller than those deeply stained.

According to M. Sée (1896) the gonococcus is $1\ \mu$ long and 0.6 to $0.7\ \mu$ wide.

Although actual measurement is not important for diagnostic purposes, yet it is advisable to have a visual impression of the size of the gonococci, as viewed through an oil-immersion lens. Occasionally one meets with other Gram-negative diplococci in urethral smears, and they are especially common in conjunctivitis. Trained observers, however, are not likely to mistake these for gonococci, as they are generally distinctly larger than the latter. For beginners, it is advisable in such cases to compare the smear in question with another smear containing true gonococci.

In smears from pure cultures of gonococci, one can frequently observe enormous differences in the size of the germ, more especially in old cultures, where a considerable amount of degeneration and autolysis has occurred. This will be discussed in a later chapter.

The Intracellular and Extracellular Characteristics.—Neisser in his first publication described the grouping of the gonococci and drew attention to their intracellular position. This is so markedly characteristic that it has been brought into prominence by all other observers as an important diagnostic feature. Later, however, with the discovery of the meningococcus, it was found that this organism shared all these characteristics with the gonococcus.

Bumm (1889), after a minute examination of carefully prepared smears of gonorrhoeal pus, concluded that the majority of the germs were situated within the pus cells. We know of no other pathogenic organism with this typically intracellular position, with the exception of the meningococcus.

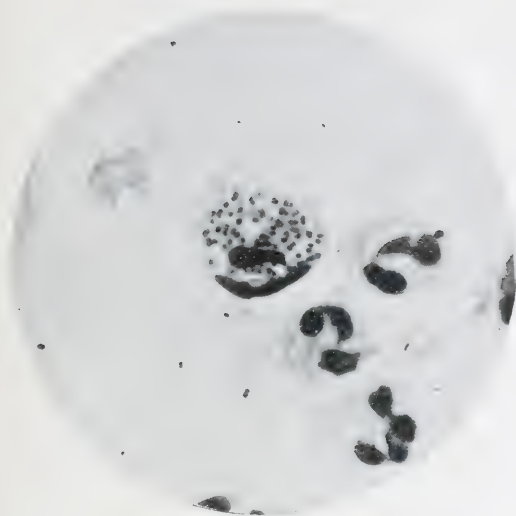
Neisser (1879) originally held the view that the gonococci were not really situated within the pus cells, but that they were only adhering to the surface of the latter.

Haab (1881), on the contrary, stated that the cocci were actually embedded in the protoplasm of the leucocytes. This opinion was supported by Leistikow (1882) and Bumm (1889), and is held by the majority of modern observers (see microphotograph No. 1, Pl. I.).

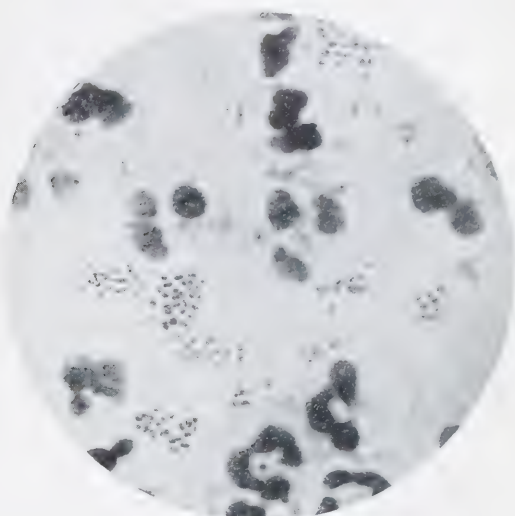
Bumm states that if the fresh gonorrhoeal pus be examined in dilute acetic acid, one can observe first that the leucocytes swell out into distinct spheres; these gradually dissolve or rupture, and the gonococci swim away with the outflowing stream of protoplasm. In this way the germs can be freed from the cells, and by subsequent staining it will be found that the cocci are quite dispersed, or that they lie scattered in the neighbourhood of the surviving nuclei.

According to Plato (1899), the intracellular position can be demonstrated by the method of intravital staining. For this purpose he recommends that a small drop of fresh gonorrhoeal pus be mixed with a dilute solution of neutral red (1 c.c. of cold saturated neutral red solution in 100 c.c. of physiological saline), and examined directly in a cover-slip preparation. It will be noticed that many of the intracellular gonococci are stained a deep red, whilst those lying extracellularly are quite unstained. By gentle mechanical pressure on the cover glass it is possible to burst some of the leucocytes packed with the germs, and as soon as the latter are discharged in the outflowing protoplasm and set free, they immediately lose their red colour. The number of gonococci situated within one leucocyte may be extraordinarily great. According to Leistikow, it may amount occasionally to 200 or 300. Scholtz considers that this is an over-estimate, and states that the largest number that can be counted is in rare cases about 100. When pus cells are packed with gonococci, they as a rule appear spherical. They seem swollen, and larger than the surrounding leucocytes. They may actually burst owing to excessive stretching, in which

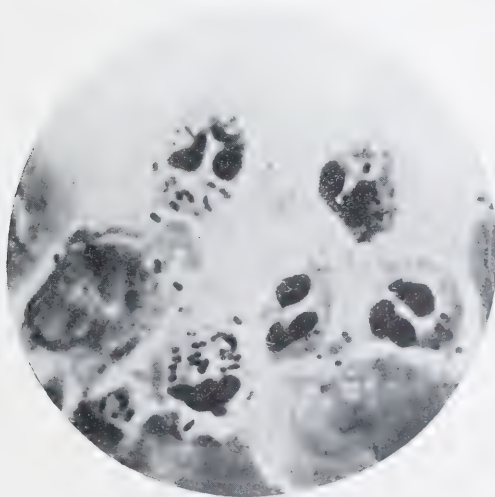
PLATE I



No. 1.—Smear from urethra of an acute case of gonorrhœa. Stained by Jensen's method. The pus cell contains about 40 pairs of gonococci. Magnification = 1000 diameters.



No. 2.—Urethral smear from acute case of gonorrhœa. Stained by Jensen's method. Note that in this case the gonococci are all extracellular. Magnification = 1000 diameters.



No. 3.—Urethral smear from acute case of gonorrhœa. Stained by Jensen's method. This case shows gonococci of a very unusual and peculiar morphology. Magnification = 1000 diameters.

case the cocci lie scattered around the remaining nucleus. One usually finds a relatively large number of these burst cells in smear preparations. The bursting in this case, however, is due, according to Scholtz, to the mechanical factor in smearing and drying the pus on the slide. Burst cells, however, can also be observed in hanging-drop preparations.

Bockhart (1883), Haab (1881), Kiefer (1896), and Foulerton (1897) maintained that the gonococci were sometimes situated even within the nucleus of the leucocytes. The great majority of authors, however—Neisser, Arning (1883), Bumm, Baumgarten, and Jadassohn (1910), etc., believe that they are present only in the protoplasm. When the cocci lie closely against the nucleus, they frequently produce indentation in the nuclear substance either by mechanical pressure or by a digestive process, in which case, according to Bumm, it can be observed that a fine bright line of demarcation exists between them. Again the nuclei may be covered over with the germs, and when viewed from above the latter may appear to have an intra-nuclear position.

The ratio of intracellular and extracellular cocci varies in different cases of gonorrhœa. It also varies according to the stage of the disease, and according to the method of preparing the smears, as already mentioned above. In the very early stage of gonorrhœa, when the discharge is mostly mucus, one finds as a rule large numbers of gonococci lying free, and only a few are found lying within the leucocytes; the epithelial cells, on the other hand, are plastered over with moderate numbers of the germs. When, however, the secretion becomes more yellow and purulent, so does the ratio of intracellular cocci increase, and when the discharge is quite purulent by far the greater proportion of the gonococci lie within the leucocytes. Towards the end of the disease, when the secretion of pus is abating, the ratio of extracellular organisms increases. In the muco-purulent discharge of chronic cases, and in the mucoid filaments found in the urine, the gonococci generally lie outside the cells. In certain rare cases of gonorrhœa one finds that the germs lie almost entirely extracellularly throughout the whole course of the illness (see microphotograph No. 2, Pl. I.).

Podres (1885), Wynn (1905), Drobny (1898), and Wyeth (1913) maintain that the disease yields more readily to treatment in those cases where the gonococci lie chiefly within the leucocytes, and that on the contrary, when they exist chiefly outside the cells, the disease is, as a rule, intractable and difficult to cure. Koch (1912) states that these observations have found no confirmation. Extracellular gonococci generally lie in little groups, and isolated pairs are only occasionally seen. In rare cases the writer has observed in the urethral discharge the constant occurrence of particularly large masses of gonococci lying extracellularly, and suggesting a kind of agglutination phenomenon. One of these cases had been treated with large doses of detoxicated vaccine (see later), and had a very large amount of antibody in his blood.

Opinion varies as to the causes and conditions which bring about the entrance of the gonococci into the pus cells. Bockhart believed that the cocci within the mucous membrane were ingested by the migrating leucocytes, and thereby carried to the surface and rendered harmless. Bumm, on the contrary, believed that the entrance of the gonococci into the cells took place in the purulent secretion on the surface. More recent researches by Orrel (1887), Guiard (1894), Crippa (1893), Pezzoli (1896), Scholtz (1899), Lanz (1900), Herz (1901), and Wyeth (1913) agree that ingestion of gonococci by the leucocytes occurs principally in the free secretion on the surface of the mucous membrane. In histological sections of the gonorrhœal mucous membrane, leucocytes containing gonococci are seldom seen in the tissues, the gonococci in the lower strata of the mucous membrane are mostly extracellular, whilst those in the purulent layer on the surface are largely intracellular.

Bumm (1889), Bockhart (1886), and Henke (1889) did not believe that the leucocytes ingested the gonococci by a process of active phagocytosis, but considered that the germs themselves migrated into the protoplasm of the cells. Scholtz (1899) and Jadassohn (1910), however, were against this view, as the gonococcus did not possess any motile power. Jadassohn considered it improbable that the gonococci spread into the pus cells by multiplication, since the leucocytes showed no evidence of being dead, and from the arrange-

ment of the germs within the protoplasm it did not appear that they had been actively multiplying.

Scholtz stated that when human pus was diluted with ascitic bouillon and mixed with gonococci, one could observe the ingestion of the latter by the leucocytes.

Also Scholtz and Plato (1899) found that, after injecting living or dead gonococci into the peritoneal cavity of a guinea-pig, a leucocytosis was produced at the site of injection, and that after even a few minutes the germs were found to be ingested by the pus cells. Plato also states that in intravital staining, only substances which have been phagocytosed by the cell take up the neutral red. The intracellular gonococci stain red by his method, and he considers this to be another point in favour of active phagocytosis. Bumm, Baumgarten, Henke, Kiefer, Foulerton, and Jadassohn believed that the gonococci could multiply to some extent within the leucocytes after they had been ingested. Jadassohn came to this conclusion because of the large numbers of the germs present in some leucocytes. He did not think it probable that a pus cell could ingest such large numbers. Scholtz, on the other hand, did not believe in internal multiplication, since, if such were the case, the leucocytes would soon show signs of death and disintegration, whereas they appear quite healthy.

It is a remarkable fact that the gonococci and leucocytes damage one another so little. The morphological and biological characteristics of the gonococci are hardly altered by the phagocytosis, and one practically never sees any evidence of digestion and disintegration of the germs within the leucocytes.

Jadassohn, and also Wyeth, emphasised the importance of phagocytosis in gonorrhœa, since in this way the gonococci, although not destroyed, are nevertheless rendered harmless and discharged with the purulent secretion. Wyeth considers that, in the treatment of the disease, the purulent discharge should be encouraged rather than checked.

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CHAPTER III

TECHNIQUE AND STAINING

MAKING OF SMEARS—STAINING SMEARS—VITAL STAINING—DIAGNOSIS OF GONOCOCCI—
DIFFERENTIAL DIAGNOSTIC STAINS (GRAM'S METHOD)—MODIFICATIONS—LIMITATIONS
OF GRAM'S METHOD—OTHER DIFFERENTIAL STAINS—DEMONSTRATION OF CAPSULE—
STAINING OF GONOCOCCI IN THE TISSUES

Technique in making Dry Smear Preparations.—It is bad practice to take a sample of urethral discharge on to a glass slide without previously cleansing the glans penis and the meatus. Several kinds of bacteria, such as staphylococci and diphtheroids, usually abound in and around the external urethral orifice. These organisms become mixed with the discharge, and by imagining that they come along with the secretion from higher up the urethra, one is apt to conclude erroneously that a secondary infection exists along with the gonococcus. Such a mistake can also be made if a dirty slide is used. Staphylococci and other organisms are frequently deposited on the slide by dirty fingers, and if the purulent secretion is spread over the soiled glass one is led to imagine that a secondary infection is present in the pus.

It is important, therefore, to carry out the following measures as a routine :—

- (1) Polish the slide with a piece of dry sterile gauze.
- (2) Cleanse the glans penis and the lips of the urinary meatus thoroughly by swabbing with sterile gauze and methylated spirit. (The foreskin, of course, should be pulled well back.)
- (3) Milk the urethra from the perineum forwards, and when a bead of pus appears at the meatus, transfer a drop of it carefully to the clean slide. This is best accomplished by means of a platinum loop.
- (4) Smear the pus over the slide in a thin and even layer, by using the edge of another clean slide.
- (5) Dry quickly in the air by waving it to and fro.
- (6) Fix the specimen by passing it three or four times over the bunsen flame, and it is now ready for staining.

Especial care must be taken to cleanse the glans and meatus when one wishes to make a culture from the pus. If this is done one can very frequently obtain a pure culture of gonococci from early cases of gonorrhœa. Similarly, if it is desired to culture or examine microscopically the urinary sediment, thorough cleansing with methylated spirit is first necessary ; the urine is then passed into a sterile flask, a portion of it is transferred by means of a sterile pipette to a sterile centrifuge tube. After it has been centrifuged at a high speed for about 15 minutes, pour off the supernatant urine and transfer the deposit by means of a sterile pipette to a glass slide, or to a culture tube if a culture is required.

It is bad practice to dry urine deposits or expressed prostatic secretion over the bunsen flame. Such fluid specimens, when dried quickly in this way, usually fail to adhere to the slide during the process of staining, and, moreover, they stain badly. It is much better to allow the fluid to evaporate slowly by placing the slide in the incubator over night. By

this procedure the dried material adheres much more firmly to the slide, and it stains better. In dried urine deposits there is always a quantity of crystalline material which interferes greatly with the staining. Clearer results are obtained if the salts are dissolved away by careful washing with distilled water, prior to staining; *vide* Jadassohn (1910) and Owings.

The Staining of Dry Preparations.—The staining of the gonococcus in dry smears presents no great difficulties. It stains well with almost all aniline dyes. One of the simplest and best is Löffler's methylene blue. It gives pretty results as well as a good contrast, since the gonococci stain deeply, and show up as dark blue or almost black specks in the interior of the protoplasm of the leucocyte, which stains very faintly. The nuclei of the cells stain more deeply than the protoplasm. Brønnum (1905) recommends staining for ten seconds with a watery solution of 1 in 10,000, since by this method the gonococci stain much darker than the nuclei.

After staining for the prescribed time, wash under the tap and dry with blotting-paper. Place a drop of cedar-wood oil on the specimen (a cover-slip is unnecessary) and examine under the oil-immersion lens. The most beautiful results are obtained when the smear is spread evenly and thinly.

Other suitable stains are dilute borax and polychrome methylene blue, fuchsin, carbol fuchsin, Bismarck brown, safranin, neutral red, thionin blue, toluidin blue, methyl green, and methyl or gentian violet.

Homberger (1900) recommends cresyl violet in a dilution of 1 in 10,000. He states that this stain has a special affinity for the gonococci, so that they colour more intensely than other bacteria. The nuclei appear a delicate blue and the gonococci reddish violet.

After staining, several authors recommend subsequent decolorisation and differentiation with alcohol or dilute acetic acid, in order to remove the excess of stain from the nuclei of the pus cells and to produce a greater contrast between the gonococci and the protoplasm in which they are embedded. Schütz (1889) recommends for this purpose 5 drops of dilute acetic acid in 20 c.c. of distilled water. Czaplewski (1903) and Hensel used 1 per cent acetic acid, whilst Eschbaum (1883) decolorised with alcohol, and Klein (1895) with alcohol ether.

Double Staining.—By using two stains the germs can be made to show up more distinctly, so that isolated gonococci can be found more easily, and the diagnosis is rendered more certain.

Schütz (1889) used carbol methylene blue differentiated with acetic acid and counter-stained with very dilute safranin.

Lanz (1894) recommends for delicate results with good contrast :—

Saturated fuchsin in 2 per cent carbolic water, 1 part.
Saturated thionin blue in 2 per cent carbolic water, 4 parts.
Mix before use and stain for 15 to 30 seconds.

Schäffer (1895) stains first with carbol fuchsin (1 in 20) for 10-20 seconds and then applies 1 per cent ethylene-diamine, to which a few drops of methylene blue are added to make it a bright blue colour. Frosch and Kolle (1896) used carbol fuchsin and safranin.

Pick and Jacobsohn (1896) recommended staining for 30 seconds with the following mixture :—

20 c.c. water.
15 drops carbol fuchsin.
8 drops concentrated alkaline methylene blue.

With this method the gonococci are stained dark blue to black, the nuclei bright blue, and the protoplasm reddish.

Lenhartz (1897) and Foulerton (1897) stained for 30 to 45 minutes with a 1 per cent

watery solution of dahlia violet and 1 per cent aqueous methyl green. v. Sehlen employed a mixture of carbol fuchsin and methyl green. Galli-Valerio employed "Bleu de Piana"—a saturated solution of methylene blue containing a few drops of saturated alcoholic thymol solution, and counterstained for 1 to 2 minutes with safranin. Lanz (1898) gives the following prescription:—

Stain the carefully-fixed smear from $\frac{1}{2}$ to 1 minute in a 20 per cent watery solution of trichloroacetic acid. This bleaches the specimen, rendering it nearly pure white. Remove the excess of acid with a short rinse in water, dry with blotting-paper, and again fix in the flame. Now stain for 2 to 5 minutes with a methylene blue solution (30 c.c. distilled water, 1 to 2 drops 5 per cent KOH, and of saturated alcoholic solution of methylene blue, sufficient to colour the mixture dark blue), rinse, and finally counterstain with weak water eosin or Bismarck brown.

According to Fränkel (1898), the intracellular cocci can be demonstrated very prettily by staining first with eosin to colour the protoplasm, then afterwards applying methylene blue to colour the nuclei and the germs. The two stains may be applied at once, as with Giemsa (a preparation of eosin and methylene blue), which stains the cocci blue whilst the protoplasm shows a reddish colour.

Pappenheim gives the following as an ideal method of differentiating the cocci from the cell nuclei:—

Methyl green (oo crystals)	0.15 gram.
Pyronin	0.25 gram.
Alcohol (absolute)	2.5 c.c.
Glycerine	20 c.c.
Carbolic acid	0.5 c.c.
Distilled water	100 c.c.

Stain for 2 to 5 minutes. The nuclei appear blue-green and the cocci dark red. According to Pappenheim, the efficiency of this method is due to the fact that the methyl green has a natural aversion for the bacteria, whilst it shows an exclusive affinity for the cell nuclei. On the contrary, the pyronin stains the germs and only colours the nuclei when applied in excess. With the marked contrast obtained it is very easy to find the cocci. Another advantage is that the solution keeps good for a long time, and does not require to be freshly prepared like many of the other mixtures. It is worth noting that with Pappenheim's stain the fibroblasts are stained bright red and the granules within the plasma cells also take on a red colour.

Löffler (1907) recommends the following method:—

1 per cent methylene blue	40 parts.
Polychrome methylene blue (Grübler)	10 parts.
0.05 per cent watery bromine-eosin solution	50 parts.

Stain for 30 seconds, rinse in water, and decolorise with the following solution:—

Absolute alcohol	177 parts.
1 per cent watery bromine-eosin B	20 parts.
Acetic acid	3 parts.

The gonococci are stained dark blue, the nuclei pale blue, and the protoplasm pale rose.

Vital Staining of the Gonococcus.—This is described by Plato (1899), Uhma (1900), and Herz (1901). Plato's method is the best known, and is carried out simply in the following way:—

Transfer a small drop of fresh gonorrhoeal pus on the end of a platinum loop to a glass slide and mix it with a drop of dilute neutral red solution in physiological saline (0.85 per cent NaCl). Plato recommends 1 c.c. of a cold saturated aqueous neutral red solution to

100 c.c. of saline. Place a cover-slip over the specimen and examine with the oil-immersion lens.

It will be noted that the nuclei and protoplasm of the pus cells remain practically unstained, whilst many of the intracellular gonococci show a deep red tint. The cell granules sometimes stain light yellow. Extracellular gonococci remain unstained, and some observers consider that those which lie intracellularly take up the stain because they are dying or dead. Plato, however, does not consider that this view is correct. He found that in hanging-drop preparations the extracellular gonococci refused to take up the stain, even after four days' exposure in neutral red solution of the above strength. He observed further in leucocytes showing amœboid movement, that so long as the cocci remained in the central granular part of the protoplasm they took up the stain; when, however, they reached the homogeneous margin they slowly decolorised, but again they become stained when the central granular protoplasm has flowed over them. He thinks that the staining is due to certain metabolic products in the leucocyte which surround the cocci when they lie in the central granular zone.

Methods for the Identification of the Gonococcus in Film Preparations.—(i.) *Diagnosis cannot be based simply on the presence or absence of intracellular diplococci*, even if of characteristic bean shape, because—

- (a) The diplococci of gonorrhœa need not be intracellular. All, or almost all, may be extracellular, as in the very early acute stage, and also in some cases of chronic gonorrhœa.
- (b) The leucocytes escaping into discharges in the genito-urinary passages can take up other organisms which, by single stain methods, are not distinguishable from gonococci.

The common practice of diagnosis by single stain methods alone is therefore not permissible.

(ii.) The gonococcus is a Gram-negative organism. The majority of micro-organisms which may be confused with it are Gram-positive. The only way to exclude these Gram-positive organisms is by the routine employment of the original Gram's method, or a reliable modification of it. *For official purposes microscopical diagnosis of the gonococcus must be by Gram's method.* Vide "Special Report" series, Med. Research Committee (1918), No. 19, p. 6.

Differential Diagnostic Staining by Gram's Method.—Gram's method is the most important of all the differential diagnostic stains. Indeed all bacteria are classified into two great groups according to whether they are "Gram-negative" or "Gram-positive."

In the course of years considerable variation has developed in different laboratories in carrying out the technique of this process.

The original recommendation of Gram (1884) consists in staining with Ehrlich's aniline water gentian violet for 1 to 3 minutes, treatment with Lugol's solution (iodine 1 part, potassium iodide 2 parts, water 300 parts) for 1 to 3 minutes, decolorisation in absolute alcohol, and counterstaining with Bismarck brown or vesuvin.

Those organisms which retain the blue stain in spite of the treatment with alcohol and subsequent counterstaining are termed Gram-positive. In this group lie staphylococci, streptococci, pneumococci, diphtheroids, etc. On the other hand, those organisms which lose the blue stain by treatment with the alcohol, and which consequently take up the counterstain, are termed Gram-negative, and to this group belong the gonococcus, meningococcus, *M. catarrhalis*, organisms of the *B. coli* group, etc. Furthermore, pus cells, epithelial cells, and mucus are Gram-negative.

It has been the experience of every bacteriologist that the original method of Gram has many possibilities of error. It is necessary to impress on beginners that mistakes are easily made by carelessness and bad technique, and by inattention to certain details with regard to the preparation of the different solutions used. The following points are important:—

- (1) *Aniline water gentian violet* requires to be freshly prepared. If more than eight

days old it stains very feebly, and in consequence Gram-positive organisms are liable to appear Gram-negative.

(2) *Iodine Solution* (Lugol's solution) keeps very well, but also tends to lose its power with age and exposure. It is important to apply this solution according to the time prescribed, viz. 1 to 3 minutes. If left on for too long a time, say five minutes or longer, it binds the blue stain so firmly to the specimen that even a Gram-negative organism like the gonococcus may refuse to decolorise, and so appear Gram-positive.

(3) *Alcohol*.—This must be absolute, i.e. 98 per cent or over. Weak alcohol, such as methylated spirit, decolorises Gram-positive organisms. Even absolute alcohol will eventually decolorise them if left on too long. Alcohol treatment, therefore, should not be continued as a rule for more than two minutes.

(4) *Counterstain*.—Gram-positive organisms which have retained the blue stain in spite of the alcohol treatment may nevertheless turn out Gram-negative, (a) if the counterstain is too concentrated; (b) if it is kept on the specimen beyond the prescribed time, or (c) if it is made up in a weak alcoholic solution. A powerful stain like fuchsin is very liable to displace the blue stain.

(5) *The Thickness of the Film*.—If a film of pus is spread out very unevenly, the thin portions stain quickly and decolorise quickly in a few seconds. The thick dense parts, however, may still remain blue after five minutes' treatment with alcohol. The end result is a mottled specimen in which the gonococci and leucocytes turn out Gram-positive in the dense portions of the film. On the other hand, the thin parts which have been over-decoloured may show Gram-positive organisms as Gram-negative.

It is quite obvious, therefore, that *it is of very great importance that all smears should be spread out evenly and thinly*. In some cases, however, where the secretion contains muco-purulent flakes, or where one has to deal with urinary sediments or shreds, it is very difficult to spread out the sample in a thin and even layer. In these the staining may not always be entirely satisfactory. With urinary sediments, in gonorrhoea of the posterior urethra and in prostatic secretions, the pus cells may be shrunk and broken up and decolorise badly. The cell protoplasm in these circumstances often takes on a darker tint than normally, the gonococci are liable to counterstain very faintly, and finally the stain is very liable to form granular deposits. In such cases the beginner may feel prejudiced against the stain, and even the expert may be at a loss with regard to the diagnosis between Gram-positive and Gram-negative organisms. The specimen may require to be decolorised with acid alcohol and re-stained more carefully. Re-staining is not very satisfactory as a rule, so it is better to make an entirely new preparation. Samples of urine deposits or of prostatic secretion give better results if dried slowly by placing them in the incubator over night. In the morning they should be fixed over the flame, and mixed gently with distilled water to remove the salts.

(6) *Fixing over the Flame*.—If this is accomplished too rapidly and the film be subjected to too great a heat, ambiguous results are obtained.

Modifications of the original Gram's Method.—Numerous modifications of the original Gram's method have been devised in order to lessen the mistakes and pitfalls that are liable to occur. Scholtz and Neisser (1903), after various experiments and consideration of all recommended improvements, adopted the following prescription:—

(1) Stain for about 1 minute with aniline water gentian violet solution (3 parts aniline oil in 100 parts of warm water—shake well, filter and add 10 per cent of concentrated alkaline gentian violet solution).

(2) Lugol's solution, $\frac{1}{2}$ to 1 minute.

(3) Absolute alcohol so long as the blue colour comes away.

(4) Rinse with water.

(5) Dilute fuchsin (1 part of 1 per cent aqueous fuchsin in 15 to 20 parts water) for 10 to 20 seconds.

The above authors, as well as Kiefer, were satisfied that one minute was a sufficient time for

the initial stain and for the iodine solution. They found that a longer application gave no better results, and that, on the contrary, the smear did not decolorise so readily and evenly. For thinly spread smears 20 to 30 seconds' exposure to alcohol was usually sufficient; where mucus flakes were present a longer time (about 1 minute) was required.

The first satisfactory advance in the method, however, was made by discarding the unstable aniline water gentian violet and using, instead, carbol gentian or methyl violet according to the formula of Czaplewski (1896). He used saturated alcoholic gentian violet 10 parts, 2½ per cent aqueous carbolic acid 90 parts. This solution remains unchanged for a long time.

Czaplewski also recommended carbol fuchsin for the counterstain (1 gram of fuchsin rubbed up in 5 c.c. carbolic acid and mixed with 50 c.c. glycerine and 100 c.c. distilled water).

Jadassohn (1910) used carbol gentian violet, and counterstained with weak safranin or Bismarck brown (3 grams of the stain in 20 c.c. warm distilled water and 30 c.c. 96 per cent alcohol; shake and filter).

Steinschneider also recommended Bismarck brown.

Wertheim (1890) and Scholtz (1903) preferred dilute fuchsin (1 part of 1 per cent aqueous fuchsin in 15 to 20 parts of water. Apply for 10 to 20 seconds).

Lumenthal (Moscow) recommends counterstaining for 10 seconds with 1 part of a saturated aqueous solution of neutral red to 7 parts of water.

Weinrich (1898) especially emphasised the importance of using absolute alcohol. He recommended the addition of anhydrous copper sulphate in order to keep it free from water. He also considered that it is important to avoid rinsing with water, so that the initial stain should be displaced directly with the iodine, and similarly the iodine should be displaced with the absolute alcohol.

Jensen (1912) showed that the intensifying action of either aniline water or carbolic acid on gentian violet is quite unnecessary, and as his method removes the greatest stumbling-block in the way of successful technique, and gives excellent and consistent results, the Medical Research Committee (1918) recommended that it be employed to the exclusion of the original Gram's method. Briefly, Jensen (1) discards the aniline water and carbolic acid; (2) increases the concentration of the iodine solution; and (3) counterstains with neutral red (see coloured Plates I. and II.).

The exact technique of Jensen's method may be described as follows:—

- (1) Make the film thin and evenly distributed.
- (2) Fix in the flame, taking care to avoid overheating. (This is guarded against by testing the heated slide against the back of the hand.)
- (3) *Let the preparation become cool.*
- (4) Stain with 0.5 per cent aqueous solution of methyl violet (6. B) for ¼ to ½ minute. (This solution remains stable for months.)
- (5) Pour off the mass of methyl violet solution, and wash away the remainder with a drop or two of *strong* Lugol's solution (iodine 1 part, potassium iodide 2 parts, distilled water 100 parts). Do not wash off with water.
- (6) Pour on a fresh quantity of strong Lugol's solution and leave for ½ to 1 minute.
- (7) Wash off the iodine solution with *absolute* alcohol (not with water).
- (8) Pour on fresh absolute alcohol (98 per cent), moving the slide from side to side, as in developing a photographic film. A third quantum of absolute alcohol may be required to complete the decolorisation.
- (9) Finally, rinse with a few drops of absolute alcohol, followed immediately, without any intervening washing in water, by a solution of neutral red. (Neutral red 1 to 2 grams, 1 per cent glacial acetic acid 2 c.c., distilled water 1000 c.c.) Stain ¼ to 1 minute.

There can be no doubt that Jensen's modification is the safest and most reliable method of carrying out Gram's stain, so that it should always be used by beginners, and in all

cases where there is any doubt whether a given organism is Gram-negative or positive. In the author's opinion the chief fault of Jensen's method is the weakness of the contrast obtained by the neutral red. This fault results in a considerable amount of eye-strain when a large number of slides require to be examined.

Aqueous basic fuchsin 0.3 per cent applied for 5 seconds, or 1 per cent aqueous fuchsin in 15 to 20 parts of water applied for 10 to 20 seconds, certainly gives a much more powerful contrast, and shows up the leucocytes and gonococci more clearly. The author in consequence, whilst admitting that the neutral red is safer, prefers the fuchsin as a contrast when a large number of specimens require to be examined, as in hospital routine work.

Burke (1921) states that the addition of sodium bicarbonate increases the value of Gram's stain as an aid in the diagnosis of chronic gonorrhœa. The alkali apparently increases the penetrating effect of the stain and causes a greater concentration of the violet dye in the Gram-positive germs. It also causes some of the Gram-positive organisms, which would otherwise appear Gram-negative, to retain the violet stain. Acids such as lactic acid, on the other hand, apparently interfere with the Gram reaction, since Gram-positive organisms fail to absorb or retain the violet dye in the presence of acid. Burke believes that the reason why old cultures of a Gram-positive germ such as the staphylococcus lose their Gram-positiveness is due to the development of acid in the cultures. Sodium bicarbonate, on the other hand, does not cause Gram-negative organisms to become Gram-positive. Burke's modification of Gram's stain is as follows :—

(1) Stain with 1 per cent aqueous solution of methyl violet. Thoroughly mix with the dye on the slide a few drops (3-8, depending on the amount of the dye) of a 5 per cent solution of sodium bicarbonate. Allow to stand for 2 or 3 minutes.

(2) Flush off excess of stain with Lugol's solution and allow this solution to act for one minute or longer.

(3) Wash with water and blot with filter paper until the surface of the film is practically free from water, but do not allow the film to become dry. The success of this stain depends largely on the proper control of this step.

(4) Decolorise with acetone or acetone and ether (1 part of ether to from 1-3 parts of acetone) until the acetone flows from the slide practically uncoloured. This usually requires less than 10 seconds. The acetone should be placed on the slide. The slide should not be immersed in the decoloriser.

(5) Blot the slide dry.

(6) Counterstain for 5 to 10 seconds with a 2 per cent aqueous solution of safranin O.

(7) Wash with water, blot and dry.

(8) Immerse the film in xylene or turpentine for several minutes or until clear.

The Limitations of Gram's Method in relationship to the Diagnosis of Gonorrhœa.

—Roux (1886) was the first to emphasise the value of Gram's method for the discrimination between the gonococcus and all the other diplococci met with in the urethra and in the vulvo-vaginal tract. Allen (1887), Wendt (1887), Steinschneider and Galewsky (1889), Hogge (1893), Kral (1894), Heiman (1895), Kiefer (1895), Hijman van den Bergh (1896), Scholtz (1903), etc., all vouch for the value of the method in gonorrhœa. On the other hand, Bunn (1885), Touton (1894), Fürbringer (1895), Posner (1904), and Caneva hold that it is not sufficient for diagnostic purposes. All modern workers, however, agree that the gonococcus is definitely Gram-negative whether the sample be taken from a culture or from a gonorrhœal discharge. The limitations of the method may be enumerated as follows :—

(1) The stain does not distinguish between the gonococcus, the meningococcus, the *M. catarrhalis*, and certain other Gram-negative but non-pathogenic diplococci which occur rarely in both the male and female genito-urinary tracts.

(2) Gram-positive cocci such as staphylococci, when taken up and digested by the leucocytes, may partly lose their Gram-positive character. This, however, practically never leads to error, since the majority of the staphylococci retain their Gram-positive character, and only

those surrounded by a vacuole and showing marked signs of disintegration appear as Gram-negative.

(3) In certain cases of chronic gonorrhœa, in scanty discharges from the posterior urethra and prostate, and in urinary shreds, the gonococci may sometimes retain the violet stain with unusual obstinacy, and appear thus to be Gram-positive.

(4) Staphylococci and pneumococci which have been growing in the culture-tube for a longer period than 24 hours tend to show signs of degeneration and gradually become Gram-negative. If one wishes, therefore, to determine the staining reaction of an organism when grown artificially, the sample should be taken from the culture-tube not longer than 24 hours after it has been inoculated. Also, in making smears from cultures, it is necessary to spread the material as evenly and thinly as possible.

Other Differential Diagnostic Stains.—Von Wahl (1903) describes the following important method for differential diagnosis :—

Concentrated alcoholic solution of auramin	.	.	.	2 parts.
" " " thionin blue	.	.	.	2 "
" " " methyl green	.	.	.	3 "
95 per cent alcohol	.	.	.	1.5 "
Distilled water	.	.	.	6 "

Stain for 5 to 15 seconds. The groundwork of the preparation comes out bright blue ; the gonococci are reddish violet to black.

The above stain can be used immediately after its preparation, and remains unchanged for a year.

von Leszcynski (1904 and 1906) recommended the following process in order to differentiate the gonococcus from other organisms :—

Dilute the pus with water and make thin smears ; dry ; fix over the flame and stain for 1 minute with—

Saturated aqueous thionin blue	.	.	.	10 parts.
Distilled water	.	.	.	88 "
Liquid carbolic acid	.	.	.	2 "

Rinse in water and counterstain for 1 minute with—

Saturated aqueous picric acid	.	.	.	50 parts.
Potass. hydroxide 1 in 1000	.	.	.	50 "

Without washing in water, treat for five seconds with absolute alcohol, rinse with water ; dry ; mount in canada balsam.

The protoplasm of the pus cells stains a yellowish straw colour. The nuclei are reddish violet. The epithelial cells are somewhat brighter. The gonococci stand out as well-defined black bodies, while the other bacteria are yellowish or rose-red.

Gram's method, however, is so far the most important of all the differential diagnostic stains.

Demonstration of Capsule.—Israeli (1921) maintains that there is a clear zone shown around the gonococcus both by Gram's stain and by Löffler's alkaline methylene blue. She believes that the gonococcus has a capsule. She states that the best stain for showing this capsule is Hiss's capsule stain slightly modified, using a 5 per cent aqueous solution of methyl violet or 5 per cent aqueous solution of fuchsin, the latter being preferable. The solutions therefore necessary for this work are a 5 per cent aqueous solution of either stain and a 20 per cent solution of copper sulphate. Her technique is as follows :—

- (1) Fix the smear by heat.
- (2) Cover the slide with the stain, and heat till it boils.
- (3) Wash with 20 per cent copper sulphate solution till no more of the colour runs off.
- (4) Dry with filter-paper.

Staining of the Gonococci in the Tissues.—It is rather difficult to bring out the gonococci distinctly in sections of the tissues. It is essential to stain the section very thoroughly, and then to decolorise cautiously with alcohol. According to Scholtz, only those aniline dyes which stain very intensely are suitable. Bismarck brown is useless for the purpose, and even watery methylene blue and gentian violet solutions are insufficient and give inconstant results. The tissues should be hardened in alcohol, in corrosive sublimate with acetic acid, or, according to Zieler (1903), in Müller's formol. Embed in celloidin (Jadassohn) or paraffin. Bumm considers that the best results are obtained by staining with strong solutions of methyl violet in toluidin or aniline water for about half an hour. The decolorisation should be conducted cautiously with alcohol so that the cocci remain completely stained whilst the nuclei are lighter in tint and the protoplasm pretty clear. Decolorisation should be controlled by microscopic examination. Touton believes that the best results are obtained with Bumm's method.

Kühne (1888) recommends staining with carbol methylene blue. He recommends the addition of a little of the stain to the alcohol used for decolorisation. By his method the cocci stand out in clear contrast to the pale and indistinct tissues.

If it is desired that the tissues should be distinctly stained as well as the gonococci, the following process is recommended by Touton :—

Stain with carbol fuchsin for 10 to 15 minutes.

Decolorise in absolute alcohol just until the tissues are seen microscopically to be clearly differentiated. Place in bergamot oil and mount in canada balsam.

Jadassohn recommends Kühne's method for distinct definition of the gonococci alone, or else staining with borax methylene blue and subsequent decolorisation with absolute alcohol. (In the case of great over-staining give a short treatment with dilute hydrochloric acid.) Jadassohn, Herbst, and Finger also recommend the following method :—

Sahli's borax methylene blue for 3 to 5 minutes.

Decolorise with distilled water containing a few drops of acetic acid for 1 to 2 minutes.

Rinse quickly in absolute alcohol. Place in xylol and mount in canada balsam.

Jadassohn, Vorner, and Bastion claim to have employed a weak solution of thionin blue with good results.

Nicolle (1895) stains with very dilute carbol methylene blue, and differentiates in 1 per cent tannin solution. Jadassohn, Veillon (1898), Raymond, and Morax (1894) got very good definition of the gonococci in the tissues by his method.

Michaelis (1901) stains the section with Löffler's blue or with concentrated aqueous methylene blue solution for 1 to 2 hours, and washes it out with distilled water. For the counterstain he uses weak eosin, which is followed by a rapid dehydration in alcohol and oil of lavender.

Wertheim (1890) stains according to Gram's method with gentian violet, aniline water, Lugol's solution, 95 per cent alcohol, and then counterstains for some minutes with aqueous methylene blue.

Homburger (1900) has recommended the use of a 1 per cent "kreslylecht" violet solution, then to decolorise with alcohol, place in aniline xylol, and mount in canada balsam. Jadassohn praises this method.

Zieler (1903) described the following process for staining in sections such organisms as gonococci, typhoid, and glanders bacilli :—

(1) Harden preferably in formalin (Müller's mixture 1 in 6) ; embed in paraffin or celloidin.

(2) Stain for 8 to 24 hours in a weak orcein solution ; orcein D. (Grübler) 1 gram ; nitric acid (B.P.) 2 c.c. ; 70 per cent alcohol 100 c.c.

(3) Wash in 70 per cent alcohol for a short time to remove the excess of orcein.

(4) Place in water.

- (5) Stain with polychrome methylene blue for 10 minutes to 2 hours.
- (6) Place in distilled water.
- (7) Thoroughly differentiate in glycerine ether mixture (Grübler).
- (8) Again place in distilled water.
- (9) Pass through alcohol 70 per cent, absolute alcohol, xylol, and mount in canada balsam.

By this method the gonococci are stained quite dark. The tissues and nuclei are differentiated from the groundwork, which is colourless or light brown in tint. Whichever method one may employ, the chief point is to decolorise cautiously, and to dehydrate with the alcohols as quickly as possible.

According to Jadassohn it is good practice to dehydrate by placing the specimen only for a moment in absolute alcohol and then to transfer it to Weigert's mixture (1 part absolute alcohol and 4 parts xylol) until all the water is removed.

According to Pick and Jacobsohn (1896), Schäffer (1895), and Lanz (1894), double staining is, as a rule, not suitable for sections.

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CHAPTER IV

THE CULTIVATION OF THE GONOCOCCUS

HISTORICAL AND CRITICAL REVIEW OF THE VARIOUS CULTURE MEDIA DEvised
FROM THE BEGINNING UNTIL THE YEAR 1910¹

COAGULATED HUMAN SERUM AND SERUM AGAR—HUMAN EXUDATES—ANIMAL SERA—
ALBUMINOUS SUBSTITUTES—OTHER MEDIA CONTAINING BLOOD—FURTHER IMPROVE-
MENTS—IMPORTANCE OF THE REACTION—THE INSTITUTION OF PHOSPHATE SALTS

THE gonococcus certainly holds the record for having had more varieties of culture media devised for its special growth than almost any other micro-organism. Bumm first cultivated it successfully in 1885, on a solidified human serum. Since that time a very large number of media have been specially devised to facilitate the isolation of this organism. This apparently indicates that each new medium in turn has been found to have some disadvantage. Either it was too troublesome to prepare, or the ingredients were too difficult to obtain, or else it was found that it did not fulfil its purpose satisfactorily. The writer cannot do better than quote the following statement from an excellent paper on this subject by Martin (1910). He says: "The number of special media which have from time to time been devised for the growth of the gonococcus is of itself an indication of the difficulties surrounding the subject. The great variety in the composition of these media, coupled with the common experience that a medium successful in one person's hands has not been equally so in others, suggests that either individual strains of the gonococci vary much in their adaptability to a vegetative existence, or that some important factor is commonly overlooked in the compounding of the culture media. Both suppositions are indeed true."

According to the experience of the writer a good culture medium will grow all strains of gonococci satisfactorily. It is important to prepare the medium exactly according to the prescription given, since sometimes slight variations, which would appear trivial, may be of vital importance. In describing the preparation of his own variety of culture medium the author will lay special emphasis on these apparently trivial points so that they may not be overlooked. One of the most important factors is the length of time that the medium is exposed to heat in the course of its manufacture. The longer it is subjected to heat, the browner it becomes. A brown medium indicating over-much heat gives inferior growths. The more clear, colourless, and transparent the medium, indicating the minimum of cooking, the better it is. Inattention to this factor alone will ruin the best medium, and render it almost worthless. It is quite possible that this alone may account for the great discrepancy of results that have been obtained with the various kinds of culture media in the past by different observers.

Coagulated Human Serum and Serum Agar.—Bumm (1885) was really the first

¹ The information in this chapter up to the end of 1907 has been extracted largely from the article by Jos. Koch in Kolle und Wassermann's *Handbuch der pathogenen Mikro-organismen*, 1912, vol. 4. Vide also Lefahler (1900).

to succeed in obtaining a pure culture of the gonococcus from gonorrhœal pus. He grew the organism on coagulated human serum, and by transferring some of the growth to a healthy urethra he was able to produce a true gonorrhœa. Previous to Bumm, attempts in this direction had been made by Bokai, Neisser, Leistikow, Löffler, Krause, Sattler, Arning, Chameron, Sternberg, Oppenheimer, Bockhart, Kreis, and Lundström. Only Leistikow, Löffler, and Krause succeeded, however, in producing a true culture of the germ. The former two maintained that the gonococcus grew excellently on coagulated blood serum. Krause succeeded in obtaining a pure culture on sheep's-blood serum, which he had inoculated with the pus from a case of gonorrhœal ophthalmia neonatorum. He incubated his successful cultures at a temperature of $32-38^{\circ}$ C., and he found that the organism would not grow at ordinary room temperature.

Bumm, as already stated, used human-blood serum, which he obtained from the placenta immediately after the accouchement.

This serum was sterilised and coagulated. He attempted to transfer subcultures to the ordinary varieties of culture media, such as beef-extract agar and gelatin, and, in spite of variations in the amount of extract, etc., he was unable to get growths to develop, although he inoculated them with large quantities of fresh material from the original human serum cultures. He found, however, that he could transfer his cultures to media consisting of ox- and sheep-blood serum, but they did not grow so luxuriantly and quickly on the latter as on the human-blood serum. After many experiments he concluded that the cultivation of the gonococcus on animal serum was difficult and uncertain.

Wertheim (1891) by the introduction of serum agar earns the credit of having founded an easy and practical method for the cultivation of the gonococcus. With the aid of serum agar he studied the biology of the gonococcus very thoroughly and minutely, and the culture elements recommended by him stand out to-day as amongst the very best. He employed the following technique :—

Several loopfuls of gonorrhœal pus were mixed thoroughly in tubes containing sterile fluid human-blood serum, part of which was diluted. The tubes were then placed in a water bath at $39-40^{\circ}$ C. The contents of the tubes were added to equal amounts of fluid agar (agar 2 per cent, peptone 1 per cent, NaCl 0.5 per cent) at a temperature of 40° C. After mixing thoroughly, these were poured into petri dishes and placed in an incubator at $36-37^{\circ}$ C. In the undiluted serum agar he found that a diffuse cloudiness developed, whereas in the diluted serum agar distinctly visible colonies appeared on the following day, which were sufficiently large to be used for subcultures. By inoculating a colony from his serum agar plate on to coagulated human-blood serum, he obtained after 48 hours a pure culture which coincided in every respect with those produced by Bumm. With the gonococcus cultures produced on serum or serum agar, Wertheim was able to infect successfully the urethra of several paralytics. After several experiments he concluded that 1 part of fluid human serum mixed with 2 to 3 parts of meat-extract-peptone agar was the most suitable proportion of the two elements. In this proportion the serum agar coagulated excellently. On such a medium whitish-grey colonies appear after a few hours; these enlarge and coalesce to form a whitish-grey slimy film over the surface. Wertheim described the growth as being very luxuriant, and much more profuse than the growths obtained on coagulated human-blood serum. He considered that the superiority of his medium over Bumm's coagulated serum was due to the peptone rather than to the meat extract constituent.

Human Exudates and Animal Sera as Substitutes for Human Blood Serum.—As it is often difficult to procure human serum, many experimenters endeavoured to substitute for it other human albuminous fluids or animal sera. Steinschneider (1890) substituted hydrocele fluid with success. Young (1900) and many others have had good results with this fluid. Menge (1893) obtained similar success with fluids from ovarian cysts and from hydrosalpinx, and McCann (1896) also recommended ovarian cystic fluid. Kiefer (1895) found that ascitic and pleuritic fluid could also be employed with satisfactory

results. Young also recommended ascitic fluid. Scholtz (1899), however, pointed out that such fluids did not possess a constant composition like human-blood serum. Their albuminous content varied considerably; and even when they did contain sufficient albumin, they often proved for some unknown reason to be unsuitable for the cultivation of the gonococcus. Scholtz therefore rightly advises that these fluids should first be tested, to prove whether they are suitable for growing the gonococcus when incorporated with extract-peptone agar, before using such a medium for diagnostic purposes.

Laitinen (1895) also maintains that ascitic fluid and the fluid from cysts cannot always be used successfully in the place of serum for the growth of the gonococcus. He states that the sodium chloride and other salts present have a certain effect as well as the albumin content. He also found that the alkalinity of cystic and ascitic fluids varied considerably, and that this was also important. His experiments showed that the fluids which had an alkalinity equal to 12 to 25 c.c. of normal soda per litre were the most suitable to add to the extract-peptone agar. (Meat extract is always too acid.)

Numerous attempts have been made to improve and simplify the Wertheim culture medium. Kiefer (1895) recommended increasing the meat-extract-peptone agar to four parts instead of three as used originally, so as to produce a firmer consistency in the medium. Koch (1912), however, maintains that Wertheim's proportion generally gives sufficient firmness, and being moister gives more favourable growths than Kiefer's modification, since the latter inclined to become too dry in the incubator. Kiefer, however, improved upon Wertheim's technique by suggesting that the gonococcal pus should be spread over the surface of the coagulated medium, instead of mixing it with the molten agar at 40° C. and then allowing the latter to solidify. He pointed out that the exposure of the gonococci to a temperature of 40° C., even for a short time, was deleterious, and tended to destroy them. Moreover, they grew better on the surface of the medium than deep down in the substance, and the colonies on the surface were more easy to recognise.

Schäffer (1895) recommended the use of spleen extract instead of ordinary meat extract. The gonococcus in his experiments grew even more luxuriantly on serum-spleen-extract agar prepared according to Wertheim's method than on Wertheim's original medium. It was noted, however, that the gonococci died off more quickly on this modification. Ascitic fluid has been largely used for the cultivation of the gonococcus instead of human serum. It is easily procurable in all large hospitals. Experiments have proved that ascitic-fluid agar is as good as Wertheim's blood-serum agar. One litre of ascitic fluid should be well shaken up with 20 c.c. of chloroform to sterilise it, and kept ready for use in small sterile flasks. When fresh culture medium is required take three parts of nutrient agar and mix with one part of ascitic fluid. Heat the mixture to 60° C. for one hour and then pour into either petri dishes or tubes. Further sterilisation is unnecessary. It is advisable to prepare the culture medium fresh, sufficient for the present requirements, as the gonococcus grows better on the moist fresh medium than on old dry ascitic agar, although according to Koch there are certain strains of gonococci which seem to grow better and more luxuriantly on the medium when it is somewhat old and dryer. In order to isolate the gonococcus from gonorrhoeal discharges, the surest method is to cleanse the glans penis and orifice of the urethra with sterile saline, squeeze out the pus, and by means of a platinum loop carefully distribute it over the whole surface of the culture medium in a petri dish. Place in the incubator and examine after 24 hours. When the gonococcus has been isolated pure and free from other germs it is advisable to subculture it on slope tubes rather than on plate culture, since the former do not dry up so quickly and they are not so liable to be contaminated. Koch and Vannod observed that the growths obtained in the slope tubes were far more luxuriant than on the plates, because the former were more moist than the latter. Koch (1912) states that an ascitic agar medium which grows one strain of the gonococcus very satisfactorily, might give poor growths with a different strain. As another illustration of this variation in the suitability of the same medium for different species of the gonococcus, he points out that some strains hardly show any growth

during the first 24 hours, and the colonies do not attain their full size until 48 hours. He is unable to explain why in such cases the growth should be delayed.

Many efforts have been made to find a good substitute for human serum and human serum exudates. Kral (1894) got successful growths with animal sera. De Christmas (1897 and 1900) claimed good results with coagulated rabbit serum and with dog serum. Besançon and Griffon (1900) recommended the use of rabbit's blood added to agar at 50° C. in the proportion of 1 of blood to 2 parts of the agar. Wertheim tried to substitute animal for human serum, but was convinced that the growths obtained were not so satisfactory. Scholtz states that even when the bactericidal properties of the animal sera are removed by heating them to 56° C., according to Steinschneider's process, no better results are obtained. Wollstein (1907) found dog-serum agar to be useless for isolation purposes, but that sheep-serum agar was good. A useful culture medium which is prepared with animal serum is the pig-serum-nutrose agar, suggested by von Wassermann (1897). According to v. Wassermann the real advantage of this medium is that the coagulating property of the serum is removed by the addition of the nutrose, and consequently the serum can be sterilised by heating. This medium is prepared as follows: 15 c.c. of hæmoglobin-free pig's serum is placed in an Erlenmeyer flask and diluted with 30–35 c.c. of water. To this is added 2–3 c.c. of glycerine and 0.8 to 0.9 gramme or about 2 per cent of nutrose. This solution is well shaken and afterwards heated to boiling point over a flame, shaking all the time. The cloudy mixture gradually becomes clear, and can be heated as long as the occasion requires for the purpose of sterilising it. With fresh serum 20 minutes is generally long enough for sterilisation. To make plates and slant tubes, mix the sterilised serum with an equal part of 2 per cent peptone agar. In general it is advisable to make plate cultures with this medium, as it is too soft and will not keep its shape in slant tubes. Scholtz criticises v. Wassermann's medium, and states that, however suitable it may sometimes be for the cultivation of the gonococcus, yet it cannot compete with Wertheim's serum agar as regards sureness and luxuriance of growth. Koch and Sieskind (1912) tested the respective values of ascitic-fluid agar and the pig-serum-nutrose agar. They found that the latter gave good growths of the gonococcus, but that it had two serious disadvantages: firstly, that its preparation was complicated and difficult; and secondly, it was too soft for the purpose of making slope cultures.

Stroos (1898) made extensive experiments with regard to the respective values of human and animal sera. He used ordinary meat-juice agar with a slightly alkaline reaction. To this he added the serum in proportions varying from $\frac{1}{4}$ to 3 c.c. (usually 1 c.c.) to 10 c.c. of the nutrient agar. He found that when human serum obtained from the placenta was added in the above proportion, the medium practically always gave satisfactory growths. Animal serum, on the other hand, gave very variable results. He tested the serum from 34 different oxen, 23 horses, and several rabbits. Some of these sera gave growths almost as good as those obtained with the human serum agar. Very few were absolutely unsuitable for the cultivation of the gonococcus. With some he obtained good growths with as little as $\frac{1}{4}$ c.c. added to 10 c.c. of agar; whereas when added in larger quantities, 1 to 3 c.c. of serum to 10 of agar, the growth was impoverished, and sometimes even inhibited altogether. His experiments show that animal serum varies very much, and this explains the contradictory reports in the literature with regard to its utility in the cultivation of the gonococcus. Stroos maintains that several animal sera contain substances which hinder the growth of the gonococcus, and is inclined to attribute this to colloidal properties and not to the salt content or reaction of the serum. He does not recommend the routine use of animal serum for the cultivation of the gonococcus.

Other Albuminous Substitutes. Several workers have attempted to find other albuminous substitutes in place of sera and serous exudates. Schrötter and Winkler (1890) claim to have cultivated the gonococcus successfully on the coagulated albumin of plover's eggs.

Steinschneider (1893) obtained some growths on urine agar, made from albuminous urine, and Finger (1894) used a mucin agar made by adding sterilised saliva. Both results were, however, unfavourable. On the other hand, Hammer (1895) maintains that albuminous-urine agar forms a successful culture medium. Wright (1895) recommends an agar containing two parts of ox serum and one part of human urine. Nastjukoff (1893) and Sée (1900) found egg-yolk albumin to be conducive to growth. De Christmas (1897 and 1900) tried albuminous-urine and chicken-albumin agar, but obtained only very poor growths or none at all.

Steinschneider (1895) maintains that egg-yolk agar is a reliable culture medium for the gonococcus, but has the disadvantage of being opaque. On the other hand, he found that meat-extract, albuminous water, and peptone were unsuitable substitutes for serum. Heiman (1895 and 1898) and Wagner both experimented with albuminous urine combined with agar; the former only succeeded in getting feeble growths of the gonococcus, whereas the latter claimed to have obtained better results. Dujol and Oliviero also used urine agar. Veillon (1898) tested the media recommended by Schrötter, Winkler, Nastjukoff, and Sée, and concluded that all of them were unreliable. He further maintains that hæmoglobin and globin are not good substitutes for serum. According to Jundell (1900) egg albumin is unsuitable. Stroos (1905), however, reported that successful growths could be obtained by employing yolk of egg and spleen extract, which he sterilised either by boiling or by heating for an hour at a lower temperature on several occasions. With other albuminous substances, such as crystallised hæmoglobin, nutrose, aleuronat, and casein, he had no success.

Lipschütz (1904) claims to have used powdered-egg albumin with success. The following are the details of his method:—A 2 per cent solution of egg albumin in water is prepared and to each 100 c.c. is added 20 c.c. of a decinormal solution of sodium hydroxide. This is allowed to stand for half an hour and shaken vigorously at intervals. It is then filtered through a Falten filter and transferred to Erlenmeyer flasks each containing 30–50 c.c. Sterilisation is effected by heating to boiling point, two or three times on the same day, or once a day on two successive days. It may also be sterilised by passing a current of steam through it, but this causes a slight decrease in the alkalinity. This albuminous liquid is colourless and transparent, and shows a distinctly alkaline reaction on sensitive litmus paper. For the cultivation of the gonococcus he recommends that one part of the albumin solution should be added to two or three parts of agar (agar 1 per cent, containing $\frac{1}{2}$ per cent of ordinary salt and 1 per cent peptone), or a liquid medium can be made by adding his egg-albumin fluid to ordinary nutrient bouillon. His medium possesses the advantage of being easily prepared, and it is also clear and transparent. According to Jadassohn (1910) the gonococcus does not grow so luxuriantly and quickly on Lipschütz's medium as it does on ascitic-fluid agar, but the growth is nevertheless very visible, and has a whitish, dry appearance.

Various other Culture Media containing Blood.—Abel (1892 and 1893) recommended Pfeiffer's blood agar, which has the great advantage of being easily prepared at any time, since it consists simply of ordinary nutrient agar smeared with blood. According to Scholtz, however, the growth of the gonococcus on Pfeiffer's medium is feeble and unreliable. He states that primary growths cannot be obtained with any certainty unless large numbers of gonococci are present in the pus, and only when secondary organisms are very scarce or absent. Primary growths sometimes occur on this medium when inoculated with pure gonorrhœal pus from abscesses or with the fluid from gonorrhœal arthritis cases. Scholtz maintains, however, that it is not suitable for proving the presence of isolated gonococci in the urethra, nor is it suitable for growing the gonococcus in quantity. Harris (1902) used Pfeiffer's blood agar successfully, but stated that it was necessary to pour the human blood liberally over the agar. Duval and Lewis (1905), in two cases of gonococcal septicæmia, got growths by smearing drops of the blood over dextrose-agar-gelatin plates. Jos. Koch experimented with various blood agars,

and concluded that horse-blood agar was a suitable substitute for ascitic-fluid agar. He used defibrinated horse blood, which he mixed with melted Chapoteaut agar (cooled to 50° C.) in the proportion of 1 of blood to 3 of agar. It can be put up in plates or tubes. Sieskind investigated the relative values of this horse-blood agar and ascitic-fluid agar. He smeared the same gonorrhœal pus simultaneously on the two varieties of media, both freshly prepared, and found that they developed a similar number of colonies. The colonies on the horse-blood agar were, however, as a rule smaller than those on the ascitic agar, and sometimes they did not develop their maximum size till after 48 hours. This delayed growth, however, may occur sometimes on the ascitic-agar plates as well. He concludes that horse-blood agar freshly prepared is suitable both in the form of plates and of tubes for the isolation of the gonococcus, and that it is also suitable for subcultures of the pure organisms. He recommends the use of horse-blood agar when there is any difficulty in procuring ascitic fluid or human serum.

The "Sang gélósé" of M. Sée (1900), which consists of rabbit's blood mixed with agar, does not appear to be very suitable for the growth of the gonococcus, and according to Scholtz this medium has not stood the test for efficiency.

Further Improvements with regard to the Nutrient Agar, and Importance of the Reaction.—For a long time it was maintained as a fact that the gonococcus could only be cultivated successfully on a medium containing human serum or some human exudate. Thalmann (1900), however, reported that he had obtained luxuriant growths of the organism on ordinary nutrient agar of a certain reaction. He claimed that the growth was visible microscopically in 20 hours and macroscopically after 24–28 hours. He was the first to point out the importance of the reaction of the culture medium, and considered that this was a more potent factor than the actual nutritive nature of the ingredients themselves. His medium consisted of meat extract (obtained by cooking meat for 15 minutes with boiling water) mixed with agar. A measured quantity of this molten nutrient agar was neutralised with caustic soda, using phenolphthalein as an indicator, until a permanent pink colour appeared. The total volume of the medium was then ascertained, and the necessary amount of soda solution was added to neutralise 70 per cent of the total. He considered that this gave the optimum reaction for the growth of the gonococcus. On this medium, however, the growth could only be maintained for one or two generations. It was therefore unsuitable for subcultures; but he considered that it was especially suitable for diagnostic purposes, *i.e.* for the primary cultivation of the gonococcus from gonorrhœal pus. For subculture purposes he recommended a mixture of one part of his $\frac{2}{3}$ neutralised meat-extract-bouillon with one part of pig's-blood serum. This fluid is coagulated in plates or sloped tubes by heating it to 70° C. He found that on this modification of his medium the colonies appeared visible to the naked eye after 16 hours. Several workers claim to have had good results with Thalmann's agar medium in obtaining primary cultures of the gonococcus from gonorrhœal discharges. Ströhmberg (1901) obtained 93 positive cultures from 95 prostitutes suspected of having the disease. The reports of Brongersma and van de Velde (1903) and Picker (1906) are also favourable. On the other hand, Baermann (1903), Rothmann (1905), Alfén (1904), and Jeckstadt (1904) had no success whatsoever with this culture medium. Scholtz (1903), by repeated experiments with meat-extract agar neutralised exactly in accordance with Thalmann's instructions, has only occasionally observed a growth of the gonococcus. The growths were at the best very feeble, and he considers that Thalmann's medium is absolutely unreliable for diagnostic purposes and entirely unsuitable for subculture work. He believes that any successful primary growth of the gonococcus on this medium is due to the fact that the medium is smeared with the albuminous purulent discharge. This albuminous pus may also be transferred to the first subculture tube, but when the medium is no longer coated with the pus it has become useless so far as further growth of the gonococcus is concerned. Thalmann himself has admitted the fact that the gonococcus grows on the primary culture made from the pus, but that further subculture is uncertain

and difficult on his medium. Baermann states that even a primary culture is difficult to obtain on Thalmann's agar unless a considerable quantity of pus is smeared upon it, and concludes that culture media containing serum are vastly superior. Kutscher (1909) was not even once successful in growing the gonococcus from gonorrhœal secretions on a medium prepared exactly according to Thalmann's prescription; on the other hand, simultaneous inoculations made on ascitic-fluid agar gave practically always positive results. With this former medium he was unable to obtain growths even when an abundant supply of the purulent secretion was used.

It is well known that one of the chief diagnostic features of the gonococcus besides its characteristic shape and staining reaction is the fact that it will not grow on ordinary agar. Urbahn (1903), however, and later Wildbolz (1906) and Vannod (1907), maintained that if the gonococcus was grown for a period of time artificially by frequent subculture on serum agar, growths could eventually be obtained on ordinary nutrient agar. They would not grow on the latter until as a rule they had been cultivated for some four to five generations on serum agar, but some strains required a much longer time. The gonococci must therefore be acclimatised, so to speak, for some time on serum agar before they are able to grow on a less suitable medium such as ordinary nutrient agar. Wildbolz used a nutrient agar consisting of beef-extract, 0.5 per cent saline, 1 per cent peptone, and 1.5 per cent agar, brought to a faintly alkaline reaction. According to Koch different kinds of ordinary nutrient agar vary greatly in value as a culture medium for the gonococcus, even although they contain the same combination of nutrient ingredients. This must be due, he says, to certain qualities not yet definitely discovered. Vannod claimed to have got good growths on ordinary nutrient agar when the medium had a slightly alkaline reaction to litmus; and although he agrees that the gonococcus will not grow easily as a rule on this ordinary agar in primary cultures, yet he was able both to isolate and to maintain a number of strains on such a medium. Vannod, however, does not claim his agar to be the best medium for the gonococcus, and indeed he states that in mixed infections it is imperative to use other media. Of these he considers Wertheim's and Wassermann's to be the best, and he agrees with Neisser and Scholtz (1903) in preferring the former.

The writer has never been able to isolate in primary culture a true gonococcus on ordinary agar media. He is therefore disinclined to believe that the gonococcus can be isolated on Thalmann's agar. He agrees, however, with the statements of Urbahn, Wildbolz, and Vannod.

Abe-Nakao (1907) recommended a medium composed of macerated beef 1 part and agar 2 parts. The beef is macerated in the ice-chest and kept for a month before use.

Wollstein (1907) got very satisfactory growths of the gonococcus on sheep-serum agar. From moist slope cultures on this medium she recovered the germ alive, after thirty-five days' incubation at 37° C. Ordinary glucose agar and dog-serum agar she found to be useless for isolation purposes.

Torrey (1907) maintains that the gonococci live longer in liquid than in solid media. He states that they remain viable for 5 or 6 weeks in ascitic broth at 37° C.

Gurd (1908) was able to grow the gonococcus satisfactorily on Duval's blood agar, which is prepared by adding 4 to 7 drops of human blood to 6 to 10 c.c. of ordinary nutrient agar at about 50° C. He got the best results when the medium was brought to a reaction of 0.6 per cent acid to phenolphthalein. Ordinary nutrient agar he found unsuitable for isolating the organism, but old subcultures could be cultivated for a short time on plain agar. He states that 5 per cent glycerine inhibits the growth of the gonococcus, but this substance is good for the *M. catarrhalis*.

The gonococcus did not grow at a temperature above 41° C. or below 32° C. Cultures on his medium when kept at room temperature were found to be dead after seven days.

Piorkowski (1908) used an egg-culture medium for the gonococcus with some success.

North (1909) claims to have got growths as good as those obtained on ascitic agar,

with a medium containing no human constituents. He used a beef-extract gelatin agar made up as follows :—

One pound of lean beef or veal is extracted with 500 c.c. of water for 18 hours. To this extract add 10 grams of agar, 20 grams of gold-label gelatin, 20 grams of dried peptone (Witte), and 5 grams of sodium chloride. Make up total bulk to 1000 c.c. with water. Titrate and bring to a reaction neutral to phenolphthalein. The gelatin agar remains solid at 37° C. He grew three strains of the gonococcus satisfactorily on this medium and subcultured them successfully for several months.

The author has not tested North's medium, but considers that his method of extracting the beef for a long time without heat is to be recommended, since there is no doubt that the less the various ingredients of any medium are heated the better.

The Institution of Phosphate Salts.—Martin (1910) made a very valuable contribution to our knowledge of the cultivation of the gonococcus, more especially with regard to the proper reaction and the value of the phosphate salts. He points out that in the early days litmus was chiefly used as an indicator, but phenolphthalein is better.

The titration of culture media, he says, should be made at 100° C., for then, in the process of sterilisation, the reaction will be less likely to be altered by the driving off of dissolved CO₂. Also electrolytic dissociation varies with the temperature, and acidity is merely an expression of the degree of preponderance of hydrogen ions over hydroxyl ions. Serum reacts acid to phenolphthalein and alkaline to methyl-orange and litmus, but serum is almost exactly neutral, *i.e.* the hydrogen and hydroxyl ions are about equal. There is no free acid or alkali in serum, these being united to the proteins. The phosphates act similarly as powerful neutralisers of free acid and alkali. This property of the phosphates led Henderson and Webster (1907) on theoretical grounds to suggest their use for the maintenance of neutrality in culture media in general, and Martin is convinced of their value in this respect. He does not think that urine is of special value, but any good properties it may have no doubt depend on its phosphate content. He points out that *v.* Wassermann's medium contains a proportion of phosphate in the form of nutrose. Sodium chloride, he says, is toxic to bacteria. It reacts acid to phenolphthalein, but just on the neutral point. Disodium phosphate (Na₂HPO₄) is faintly alkaline, a 1 per cent solution being 0.25 per cent alkaline. Monosodium phosphate (NaH₂PO₄) is distinctly acid, a 1 per cent solution being 7 per cent acid. Martin maintains that phosphate acidity is non-toxic or very little so to bacteria. *B. coli*, *B. typhosus*, *B. diphtheriae* and *Staph. aureus* can grow well on agar in which the phosphate acidity is 13.5 per cent to phenolphthalein. The cholera vibrio grows well up to 2.5 per cent acidity. The gonococcus grows feebly at 2.5 per cent acidity, and will not grow at all at 5 per cent acidity; on the other hand, the gonococcus will not grow on a medium that is faintly alkaline to phenolphthalein. Serum on the average is 0.65 per cent acid to phenolphthalein. The American Public Health Association in 1898 adopted 1.5 per cent acidity to phenolphthalein as the standard for general bacteriological work. Chester (1901), however, suggested 0.5 per cent acidity as best, as he had observed that the higher degree was unsuitable for the growth of many delicate organisms.

Martin, like Gurd, adopts an acidity of 0.6 per cent to phenolphthalein, *i.e.* + 6 acid according to Eyre's scale, as being the most suitable for the growth of the gonococcus. His medium contains the following ingredients :—Beef extract containing 0.5 per cent of disodium phosphate (Na₂HPO₄), 1 per cent of Witte's peptone, and 2 per cent of powdered agar is titrated at 100° C. and brought to a reaction of 0.6 per cent acid to phenolphthalein. He points out that if egg-white is used for clearing, one should allow for the fact that it is usually more acid than the medium. In the case of slope tubes he adds 3 or 4 drops of sterile heated (57° C. for 1½ hour) human serum. For plates he adds 2 c.c. of the human serum to 5 c.c. of the agar at 45° C. He does not consider that the hæmoglobin constituent of the blood is of special service. He says also that the medium most rich in albuminous material is not necessarily the best, because while small amounts of heated

(57° C.) human serum markedly accelerate growth, large proportions have a distinctly bactericidal action on the gonococcus. Finally, he found that in an atmosphere of pure hydrogen the growth of the gonococcus is much inhibited, but not entirely suspended, and he refers to Vannod (1907), who found that no growth at all took place *in vacuo*, where possibly the gonococci were ruptured. He agrees with Vannod (1905) that certain strains of gonococci can be isolated and maintained on plain agar.

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CHAPTER V

THE CULTIVATION OF THE GONOCOCCUS—*continued*

CRITICAL REVIEW OF THE CULTURE MEDIA DEvised FROM 1910-1922

EFFECT ON ANTIGENIC PROPERTIES—FLUID-EGG MEDIUM—MILK-WHEY MEDIUM—BEER-WORT MEDIUM—RESISTANCE TO LOW TEMPERATURES—TESTICULAR EXTRACT MEDIUM—STARCH MEDIUM—POTATO EXTRACT—TRYPTIC PEA EXTRACT—OXYGEN PRESSURE—COLE'S TRYPTIC MEDIUM—METHOD OF TITRATION BY ESTIMATION OF HYDROGEN-ION CONCENTRATION—GROWTH HORMONES AND VITAMINS—STAB CULTURES

VAN SAUN (1913) contributed a paper on the **effects of variations in media on gonococcus antigens**.

She had noticed that the antigenic and anticomplementary properties of gonococcus antigen, as used in the complement-fixation test, varied very much, and she thought that this variation might be due to the culture medium employed. In her experiments she employed ten strains of gonococci and four kinds of media of varying reactions, viz. : (1) Neutral glucose-ascitic agar ; (2) neutral-veal agar ; (3) veal agar 0.5 per cent acid ; (4) veal agar 0.5 per cent acid + 5 per cent glycerine.

Her results seemed to indicate that the most favourable antigenic properties were obtained from strains grown on the neutral-veal agar. She states that good growths seem to be favourable for good antigen, although a good growth does not always mean a good antigen. She says that agar which is in the least dry is useless for the cultivation of the gonococcus.

It appears to the author that much further research is required on this subject before any definite conclusions can be made. It is worth noting that she obtained quite good growths on the veal agar containing 5 per cent glycerine, a substance which, according to Gurd, inhibits the growth of the gonococcus.

Besredka and Jupille (1913) devised a **fluid-egg medium** for the gonococcus. Their prescription is the following :—

White of egg beaten up with 10 volumes of distilled water	.	.	4 parts.
Yolk of egg beaten up with 10 volumes of distilled water	.	.	1 part.
Ordinary meat bouillon	.	.	5 parts.

Strain through a cotton cloth and heat to 100° C. to hurry the precipitation, then filter through a Chardin paper. Transfer to tubes or flasks and sterilise at 115° C. for 20 minutes.

They have recovered the gonococci alive from this liquid medium after 22 days at 37° C., and they recommend the use of this egg bouillon for keeping the germ alive for a long time.

Weil and Noiré (1913) employed the **milk-whey culture medium** recommended by Sabouraud and Noiré for staphylococci. It is prepared as follows :—

- (1) Precipitate the casein of 1 litre of milk by adding 2 c.c. of hydrochloric acid.
- (2) Filter the whey through a damp cloth and neutralise with normal sodium hydroxide.
- (3) Add one-half of its volume of 2 per cent peptone water, also 1 per cent saccharose, 0.35 per cent to 0.4 per cent urea, and 1.6 per cent agar.
- (4) Sterilise and filter.

The culture tubes should be inoculated copiously with the gonococcal pus and then placed immediately in the incubator.

They consider that this medium is an advance on the previous culture media used for the gonococcus, and state that it is very superior to the ascitic agar of Wertheim, both with regard to primary and subcultures. They claim that the gonococcus remains viable in the culture tubes for 15 to 20 days.

Lumière and Chevrotier (1913) originated a new culture medium, the chief constituents of which consist of **egg albumin and beer-wort**. Six grammes of the white of an egg are added to 1000 c.c. of beer-wort and heated to 115° C. in the autoclave. After hot filtration, render alkaline and sterilise again at 110° C. for 10 minutes. It is recommended, though not absolutely necessary, that 1 c.c. of horse or donkey serum be added to each 15 c.c. of the medium. They state that cultures of the gonococcus can be obtained on this medium from pus which has stood for 8 hours at room temperature.

In a later paper (1914) these authors state that most of the workers who have used their medium have obtained very excellent results, though some had no success with it. They consider that the cause of failure in these few instances is due to the fact that the beer-wort is not a definite, constant product, but varies considerably in its composition. It is necessary to use the beer-wort obtained from barley malt, with or without hops, and free from excess of other starchy material, sugar, or chemical products. Some beer-worts contained about 110 grms. of sugar products per litre, and, as they found that 22.5 to 55 grams of these products per litre gave the most favourable results, it is necessary to dilute such beer-wort to one-quarter or half strength.

They recommend that this medium should be inoculated with several drops of the gonococcal pus.

In two further articles (1914) they discuss the viability or vitality of the gonococcus on their culture medium under varying conditions such as absence of air and at low temperatures. Previous workers had been unable to obtain growths of the gonococcus *in vacuo*, and had found that the organisms died quickly at low temperatures. Lumière and Chevrotier, however, obtained growths on their medium in absence of air, when the air was excluded by a layer of oil and also *in vacuo*.

Under ordinary conditions at 37° C. the gonococci remained alive on their medium for 27 to 28 days. Growths in the absence of air, by using a layer of oil or *in vacuo*, were very much slower in developing, but the viability was prolonged for about four months. They found that currents of sterile air or pure oxygen did not injure the germs, and they conclude therefore that the death of the gonococcus is not due to the action of oxygen alone. Filtrates of the autolysed germs were found to be detrimental to growth, the greater the amount added, and they conclude that the viability of the organism is destroyed by its own oxidised toxin. These are important observations, but the author does not entirely agree with their interpretation of them. In the course of the writer's own researches it has been noticed that generally the gonococci remain viable for a longer time on those culture media on which they grow slowly, and *vice versa* they tend to die off more quickly on a medium which is so suitable that they grow with great profuseness. It would seem that their death is due to the excess of their own toxin, produced in the process of profuse growth, and also to exhaustion of the medium. A medium therefore on which they remain viable for a long time does not necessarily mean a good medium. It indicates rather a mediocre nutrition where growth is slow and not profuse. On the author's plasma-agar medium, where the growths obtained are exceedingly profuse and rapid, the gonococci die off in about a week on slope cultures at 37° C. On the other hand, if stab

cultures are made, the growths obtained in the track of the stab are very slow, but the germs under these conditions remain alive for several months. It is quite evident, therefore, that oxygen or air is necessary for profuse growth, and that, *vice versa*, its absence has a marked inhibitory effect. This slowing down of the growth, however, means less rapid production of the toxin and less rapid exhaustion of the medium and hence greatly prolonged viability of the culture. It is hardly necessary to assume that the death of the organism is due to oxidation of the toxin.

With regard to the **effect of low temperatures**, Lumière and Chevrotier have been the first to demonstrate, contrary to the experience of all other workers, that the gonococci can survive for considerable periods of time in culture tubes placed in the ice chest, and even at very much lower temperatures. These authors found that a series of 9 strains of gonococci grown on their medium at 37° C. and then placed for 48 hours at a temperature of -17° C. to -20° C. were still alive, since successful subcultures were obtained. When left at -20° C. for 10 days they were still found to be alive. Another series of cultures were placed for 24 hours in a temperature at 195° C. below zero, and then successful subcultures proved that they had retained their viability, and finally a series of cultures left for several months at ordinary room temperature did not lose their original morphological or micro-chemical properties, as would have happened if kept at 37° C.

The author has been able partially to confirm these important observations on the effect of low temperatures. A 24 hours growth of the gonococcus on his plasma agar medium was placed in the ice chest for 12 days. A subculture was then made on a fresh slope tube and placed in the incubator at 37° C. No growth appeared until the fourth day, when several large colonies suddenly developed. It would appear therefore that cold, like the absence of oxygen, does not entirely destroy the gonococcus, but it inhibits its growth, and on this account it may also be employed for obtaining a prolonged viability of the cultures.

Clark (1913) published an article on "An Easy Method for the Cultivation of the Gonococcus." He prepares his medium as follows:—

(1) 500 grammes of lean beef is freshly minced and mixed with 1000 c.c. of distilled water and allowed to stand overnight in the ice box.

(2) Filter and make up the filtrate to 1000 c.c. with distilled water.

(3) Add agar equal to $1\frac{1}{2}$ per cent and boil for 15 minutes. Then add 2 per cent glucose, titrate and reduce the reaction to 6 acid (Eyre's scale) by the addition of the necessary amount of normal NaOH. No peptone or salt is required.

(4) Transfer to test tubes and sterilise. To each tube of the medium add 4 or 5 drops of fresh sterile human blood serum, slope and incubate over night to see if sterile.

He states that 16 hours after inoculation with gonorrhœal pus, the colonies of gonococci appear as fine white points.

The writer has not tested this medium, but approves of the method of making the beef extract without heat.

Dujol (1913), in a thesis on the cultivation of the gonococcus, reviewed many different varieties of culture media, and concluded that the best were the human blood agar prepared according to the method of Besançon and Griffon, also Menge's cystic fluid agar, and ascitic-agar. He considers that meat bouillon containing human serum forms the best liquid medium.

Victors (1914) published an article on the "Artificial Cultivation of the Gonococcus." The author has been unable to obtain access to this paper.

An article by Gache (1914), "Nuevo medio de cultivo del gonococco," is merely a description of Lumière and Chevrotier's medium.

Hirschfelder (1914) added a new variety of culture medium composed of the following ingredients, including **testicular extract**:—

(1) Grind up 200 grammes of bullock's testicle with a sausage grinder and boil with

1000 c.c. of water. Render alkaline with NaOH, such that 10 c.c. requires 1 c.c. of decinormal acid to neutralise it (using phenolphthalein as indicator).

(2) Filter.

(3) Make up veal phosphate agar as follows :—

Veal bouillon	1000 c.c.
Saturated solution of sodium phosphate made neutral to phenolphthalein with phosphoric acid	100 c.c.
Agar	30 grammes.

(4) Add one part of the testicular extract to three parts of the veal phosphate agar, tube and sterilise in the autoclave.

The author has not tested the efficacy of this medium. The extract of testicle should contain suitable substances for the growth of the gonococcus. The phosphate constituent is good. The reaction of the completed medium is not stated.

Warden (1915), in his "Studies on the Gonococcus," came to the conclusion that the organism rapidly autolysed on all culture media, and that this lysis was due to the presence of water. He declares that the gonococcus is much more viable on a very dry culture medium, and that it dies off quickly in liquid media. In these opinions, however, he stands alone, as practically every writer on the subject recommends a moist culture medium if prolonged viability is desired, and nearly all state that they live for long periods of time in liquid medium.

Warden used a medium composed of salt-free veal broth containing 2.25 per cent agar, rendered neutral to phenolphthalein and to which he added 5 per cent of defibrinated rabbit's blood. Before inoculation he recommended that the culture slopes should be allowed to dry in the incubator until all the water of condensation had evaporated.

Ohlmacher (1915) used Löffler's blood serum as a culture medium for the gonococcus. He found that it was possible to increase the interval of making subcultures from 7 to 14 days or even longer by inoculating the growth into the water of condensation. The new growth spreads up slowly from the condensation fluid, and the next subculture should be made from the advancing margin of growth.

Vedder (1915) states that he gave up the salt-free veal agar recommended by the New York Board of Health because subcultures had to be made every two or three days in order to keep the gonococci alive. He was the first to employ a **starch medium** for this organism, and he claims that it has given better growths than any other medium he has used.

The following is his prescription :—

(1) Make up beef extract in the ordinary manner.

(2) Add agar 1.5 per cent to 1.75 per cent.

(3) Cook, clarify and filter according to the usual method.

(4) Neutralise so that it is 0.2 per cent to 0.5 per cent acid to phenolphthalein.

(5) Add 10 grammes of ordinary commercial corn starch which has previously been emulsified in a mortar with some of the hot medium.

(6) Boil for a few minutes, tube and sterilise at 15 lbs. pressure.

No peptone or salt is added, as he found that the gonococcus appeared to grow better without these ingredients. Commercial meat extracts were not so good as those freshly prepared in the laboratory. Corn starch was found to be better than the starch of tapioca, wheat, or potato. He claims that the growths on this medium are profuse and suitable for the preparation of antigen, that satisfactory primary cultures are obtained from the gonococcal pus, and that the cultures have a long viability. Tubes kept in the incubator for several days, then placed at room temperature, were found to contain live gonococci after 40 days, and subcultures can be obtained with certainty after 20 days. It can also grow successfully the tubercle and leprosy bacillus, also streptococci and pneumococci. He considers that starch is a superior ingredient to sugar.

Broughton-Alcock (1915) described an aberrant strain of the gonococcus which grew well on ordinary nutrient agar, even in the primary isolation. He found it necessary, however, to smear the medium profusely with the material. The cultures died after 48 hours in the ice-chest, but were not killed by heat at 40°-45° C. for one hour. Heating to 50° C. for half an hour proved fatal. Cultures kept at 37° C. remained viable for two months.

This aberrant strain only fermented glucose in ordinary meat peptone broth.

Hall (1916) used a **testicular infusion agar** prepared as follows:—

(1) Mix 500 grammes of finely ground bullock's testicle (free from tunica vaginalis) with 1000 c.c. of distilled water and allow to soak over night at room temperature.

(2) Heat to 50° C., and keep warm for one hour by placing it in the incubator at 37° C.

(3) Boil, strain, and restore to 1000 c.c. with distilled water. If in excess do not reduce by boiling, since overheating is injurious.

(4) Add 2 per cent peptone (Witte's or Difco), 3 per cent agar chopped fine, 0.5 per cent glucose, and 0.3 per cent acid sodium phosphate.

(5) Soak at least one hour to soften the agar. Melt in the autoclave at 10 lbs. pressure for 30 minutes.

(6) Titrate with phenolphthalein when hot and add sufficient sodium hydroxide to neutralise it.

(7) Transfer to tubes and autoclave at 10 lbs. pressure for 30 minutes.

(8) Slope the tubes or pour into petri dishes.

He recommends that the slope culture tubes should be dried in the incubator for two days before use. It should be noted that he uses 3 per cent agar which is of firm consistence. The author also prefers a firm agar, as it appears to enable the growth to spread better over the surface. The author has found that Hall's medium is satisfactory. The testicular extract is good, also the addition of glucose and phosphate.

Bristol (1916) states that the gonococcus requires for its growth glycoproteins (preferably human) from mucin or related compounds. Ascitic, cystic, or hydrocele fluids, also blood serum and urine, all contain mucoid substances of the conjugated protein group.

Roos (1916) recommends the use of a **potato extract medium** as being very suitable for prolonging the viability of the meningococcus, hence it is very useful for maintaining stock cultures. He does not say whether or not it is suitable for the gonococcus, but the writer has included it here, as most good media suitable for the meningococcus can grow the gonococcus or *vice versa*.

The following are the steps in the preparation of Roos's medium, which is a modification of the potato blood agar medium used by Bordet and Gengou for the isolation of *B. pertussis*.

(1) Potato extract:—

- | | |
|---|--------------|
| (a) Peeled potato cut into small pieces and washed in running water for 2 hours | 100 grammes. |
| (b) Water + 4 per cent double-distilled glycerine free from acid | 200 c.c. |
| (c) Mix and autoclave for 40 minutes, allow to stand over night, and strain through a cheese cloth. | |

(2) Mix up the following in an Erlenmeyer flask:—

- | | |
|---|------------|
| Potato extract | 50 c.c. |
| Sodium chloride, 0.65 per cent solution | 150 c.c. |
| Agar | 5 grammes. |

(3) Heat in steriliser until the agar is melted— $\frac{1}{2}$ to 1 hour.

(4) Tube without filtering and sterilise in the autoclave for 40 minutes.

(5) When required for use, melt the agar and cool to about 45° C., add the desired amount of sterile defibrinated horse blood.

Roos states that this medium gives a relatively slow growth of the meningococcus with apparent suppression of ferment formation, thus resulting in prolonged viability.

It is only necessary to make subcultures every 13 to 15 days, and if the plugs are paraffined to prevent evaporation and drying, the germs will remain alive for 6 weeks. In an atmosphere of hydrogen the growth is slower, but the viability is prolonged for ten weeks.

Another medium which has been used extensively for the cultivation of the meningococcus is the *Tryptic-pea-extract agar*. It is also suitable for the gonococcus, and is usually prepared in the following way.

Trypsinised Pea-Extract Agar ("Trypagar") (Gordon and Hine).

A.—PREPARATION OF SALINE PEA EXTRACT.

Take 100 grammes of pea-flour (Pearce Duff's) and add 1 litre of distilled water with 100 grammes of salt. Mix and steam for half-an-hour, stirring occasionally. Allow to settle and filter, then sterilise and label "Saline Pea Extract." This pea-flour extract should preferably be freshly made for each batch of agar. The filtering should be done through an English make of Chardin's filter paper, which may be obtained from Messrs. Baird & Tatlock; ordinary filter paper or wool must not be used. The quality of the pea-flour is of great importance. The extract may be tested by adding one drop of concentrated HNO_3 , when a heavy precipitate forms which should dissolve in excess of the acid. This test, however, is not of very much value; the only real test is that of "growth" when the extract is made up with the medium.

B.—PREPARATION OF TRYPSIN BROTH (DOUGLAS).

Take some fresh bullocks' hearts, free from fat and vessels, mince the meat very finely and weigh. To each half kilo. add 1 litre of water, and make distinctly alkaline to litmus with 20 per cent KOH solution. Heat this slowly to $75^{\circ}\text{--}80^{\circ}\text{C.}$ for five minutes. Cool to 37°C. and add 1 per cent of liquor trypsinæ co. (Allen & Hanbury's) and keep it at 37°C. for three hours. (The trypsin preparation mentioned should be used, as several others have not proved satisfactory.) When trypsinising is finished, test for peptone in the following manner: Take 5 c.c. of broth, add 0.1 c.c. of 5 per cent solution of CuSO_4 ; mix, and then add 5 c.c. normal NaOH; a true pink colour indicates that trypsinisation is sufficient; a bluish-purple shade that it is incomplete. Then render slightly acid to litmus with glacial acetic acid and bring slowly to the boil for a quarter of an hour. Leave covered overnight in a cool place and siphon off the clear liquid in the morning. Make this broth distinctly alkaline to litmus, and (if not to be used at once) sterilise in an autoclave at 118°C. for one hour on each of two days. The necessary addition of acids and alkalis must be carefully made, little by little, so that there shall be no excess of either.

C.—PREPARATION OF FIBRE AGAR.

Weigh out the required quantity of fibre agar, cut up small with scissors, place in a large flask or enamel pail, and wash twice quickly in water. Drain thoroughly, add water just to cover, and put in glacial acetic acid to 0.25 per cent. Mix well and leave for a quarter of an hour. Pour off the liquid and wash *thoroughly* four or five times to make sure that all the acetic acid is washed out. Drain carefully.

D.—TO MAKE TRYPAGAR.

Take a measured quantity of the trypsinised broth, add 1.75 per cent agar fibre prepared as above, and 0.125 gramme of calcium chloride per litre. Autoclave at 118°C. for three-quarters of an hour to dissolve the agar. Titrate 20 c.c. of the medium diluted with 20 c.c. of water with $\frac{N}{10}$ NaOH while boiling, using *a*-naphtholphthalein (0.04 per cent in 60 per cent alcohol) as an indicator, adding with a glass rod a drop of the medium to a drop of the indicator at a time on a white tile till the first transient flush of bluish-green occurs; read off the amount used from the burette. Then go on with the titration again, adding 0.5 c.c. of 1 per cent phenolphthalein in 99.8 per cent alcohol to the medium and continuing until the first faint pink colour appears; take this reading also. The mean of these two readings gives the point to which the medium must be adjusted, and the requisite amount of 10 N NaOH (dekanormal) is then added to the bulk of the medium. This medium should now prove alkaline to *a*-naphtholphthalein and acid to phenolphthalein. Cool to 60°C. , add white of egg (2 to a litre), beaten

up well; autoclave again at 118° C. for 75 minutes (or in the steamer for two hours). Filter again through the Chardin's filter paper supplied by Baird & Tatlock, add to the filtrate 5 per cent of the sterile pea extract, and sterilise in the ordinary way. This medium must not be steamed more than necessary, as it gives off ammonia in steaming, which alters the reaction if done too often.

For the cultivation of both the meningococcus and the gonococcus, it is advisable to add 2 per cent of a sterile 5 per cent hæmolyzed solution of rabbit's blood in normal saline, etherised by the addition of 10 per cent of ether.

The author has found that this medium grows the gonococcus moderately well. It could probably be improved very much by using sodium phosphate instead of sodium chloride, also by bringing the reaction to +6 acid, and by using much less heat in the process of preparation.

Watabiki (1916), after long experience with the cultivation of the gonococcus, maintains that blood agar and blood bouillon are the most suitable with which to obtain excellent results. However, if blood cannot easily be obtained for the purpose, then **whey agar or whey bouillon** can be used as substitutes for the solid or liquid blood media. He prepares the whey agar in the following way.

200 c.c. of cow's milk are warmed to 60° C. and 5 per cent hydrochloric acid is added drop by drop, the milk being shaken to cause precipitation of the casein. It is then filtered through filter paper, and to the filtrate is added 10 per cent caustic soda solution up to the point of slight alkalinity. Two grammes of urea are now added, and the clear colourless fluid is sterilised at 60° C. for 30 minutes every day for three days. This sterilised fluid is then mixed with melted 3 per cent nutrose agar at 45° C. in the proportion of one part of the fluid to two parts of agar. Plates or slope tubes are prepared as needed. The medium must be incubated before use to make sure that no micro-organisms have gained access during preparation. When fluid medium is required, equal parts of the fluid and of ordinary broth or peptone water are mixed. It is very necessary that the fluid should not be heated above 70° C., as unsatisfactory results frequently follow the use of the fluid heated at a higher temperature. For the precipitation of casein the amount of acid necessary is not constant, as the different samples of milk undoubtedly vary in quality. This medium is a modification of that recommended by Weil and Noiré.

Wherry and Oliver (1916) state that the **oxygen pressure or tension** is an important factor in the cultivation of the gonococcus. According to them it is a "micro-aerophile" or partial oxygen tension organism. In other words, the optimum oxygen tension is less than the oxygen pressure in the ordinary air. The partial or optimum oxygen pressure necessary is produced in the culture tube by introducing a smaller tube containing actively growing *B. subtilis*, according to the method first introduced by Nowak (1908). The outer culture tube is hermetically sealed. The above authors employed Martin's culture medium, and they found that the gonococcus grew much more profusely in the tubes containing partial oxygen tension than in those to which the ordinary air had access. Also in primary cultures a very much larger number of colonies were obtained from the gonococcal pus when grown under partial oxygen pressure. The viability of the cultures grown in this way was as long as 15 to 19 days at 37° C.

They state that the natural oxygen tension in the human tissues is less than 21 per cent oxygen, and that the gonococci take some time to become adapted to the aerobic conditions of the ordinary culture tubes. They consider that growth at the optimum oxygen tension may be important. Beijerinck (1907) pointed out clearly that the character of the fermentation of germs, *i.e.* the end products, was controlled chiefly by the temperature and the oxygen pressure, so that under artificial and unnatural conditions one gets eventually different characteristics.

It has always seemed to the author that the natural virulent and antigenic properties of the gonococcus would be maintained most successfully on a medium which contained as nearly as possible the constituents of the human tissues most susceptible to attack,

and in view of the above statements it is just possible that in this matter the oxygen tension is also of importance. Pasteur (1883) concluded that viruses can vary in their multiple physiological properties according to the medium wherein they live and multiply.

Mezinescu and Holban (1919) state that although cultures of the gonococcus can be obtained on ascitic agar medium of neutral or faintly alkaline reaction, the results are very much better when the reaction is distinctly acid. The optimum reaction arrived at by titration against normal NaOH with phenolphthalein as indicator is from +1.5 to +2 per 100. A large proportion of the strains grew only feebly when the reaction was less than +1. On the other hand a reaction above +2.5 had a distinct inhibitory influence on growth. Cultures grown on artificial media from 2 to 16 months (5 to 25 subcultures) were capable of setting up an acute urethritis when injected into the urethra. Even on an acid medium the gonococcus dies out in a few days at room temperature.

Ruediger (1919) recommends a medium consisting of **veal broth** (1 part of veal to 2 parts of water) made neutral to phenolphthalein, agar, salt, peptone, and 10 per cent human blood for the isolation of the gonococcus. The cultures should be stopped with airtight plugs. Salt appeared to be an unnecessary constituent. Peptone was necessary, whereas glycerol or dextrose appeared to be unfavourable additions. The growth is said to be nearly as profuse as that of *B. typhosus* on ordinary agar.

Chapin (1918) states that an atmosphere of **10 per cent CO₂** favours the growth of the gonococcus.

Maitra (1919) claims that the gonococcus is best cultivated under reduced oxygen tension. With this method he got primary cultures on Löffler's serum and on urine agar containing egg yolk, provided a considerable amount of the gonococcal pus is smeared on the surface of the medium. Better growths, however, were obtained with media to which fresh unheated human serum was added.

Herrold (1920) got good results in isolating the gonococcus in primary culture on plates kept under partial oxygen tension in the following manner. One petri dish is inoculated with gonococcal pus, and another with *B. subtilis*. The two petri dishes are then placed together with the open ends facing each other. They are held together and rendered air-tight by means of a rubber band two and a half inches wide. Instead of reducing the oxygen tension by the use of *B. subtilis*, one petri dish may be charged with a little sodium bicarbonate and a few drops of sulphuric acid. After the plates are sealed together, the acid is allowed to run over the sodium bicarbonate and CO₂ gas is thereby produced. He used "bactoveal" phosphate agar to which ascitic fluid or goat blood was added. Gonococci were cultivated from all acute urethral discharges, and in several chronic cases where the germs could not be detected in smears. Parallel plates exposed to full air tension developed fewer and smaller colonies.

Swartz (1920) states that the oxygen tension is very important for the cultivation of the gonococcus, and attention to this is essential for profuse growth. A reduction of 10 per cent in the normal atmospheric pressure is sufficient.

Swartz, Shohl and Davis (1920) estimated that a partial oxygen tension of 10 per cent reduction gave the best growths. The gonococcus also liked moisture and seemed to thrive best at a hydrogen ion concentration of p_H 6.6 to 8.0. In culture media containing dextrose the acid end point for the gonococcus is p_H 5.6.

Jenkins (1921) found that an agar medium containing 10 per cent of whole blood and brought to a reaction of +4 to +5 acid (Eyre's scale) was satisfactory for the growth of the gonococcus. Later he used a blood plasma medium similar to the writer's medium (see next chapter) with success.

Cook and Stafford (1921) found that stock cultures of the gonococcus grew satisfactorily on testicular agar. The most satisfactory medium for the isolation of primary cultures was in their experience "chocolate blood testicular agar."

Erickson and Albert (1922) found that testicular agar containing blood and brought to a reaction of p_H 7.4 to 7.8 was the most favourable medium for the isolation and

cultivation of the gonococcus. The testicular infusion agar is prepared according to Hall's method (see before), and to this is added 0.25 to 0.5 per cent of human blood or 1 to 5 per cent of defibrinated rabbits' blood. The blood or serum is necessary for isolation, but not for securing the growth of subcultures.

Cole and Lloyd (1917) made a valuable contribution to our knowledge on the cultivation of the gonococcus.

Their researches led them to believe that there are three important factors concerned in the growth of this organism, namely :—

- (1) The concentration of hydrogen ions, *i.e.* the "reaction."
- (2) The concentration of amino-acids.
- (3) The presence of certain growth hormones or "vitamins."

They state that the great test of a good medium is its power of producing a large number of colonies when sown from a weak dilution or emulsion of the germs in saline or broth. This is what they term "dilution" sowing in contradistinction to "direct" inoculation.

In discussing the optimum "reaction," they point out that the older methods of titration are inaccurate and cannot give uniformity of results, since these methods ignore the influence of the "buffer" content, which can cause marked variation in the hydrogen-ion concentrations of the "adjusted" media, even though the titration values may be identical. Such substances as phosphates, citrates, borates, and acetates are called "buffers," because their presence in a solution or medium stabilises the hydrogen-ion concentration, so that the addition of a small amount of acid or alkali causes only a minimum of change in this concentration. On the other hand, if the medium is poor in "buffers," a minute trace of alkali or acid, for example, even exposure to the CO_2 of the air might cause a considerable change in the hydrogen-ion concentration. In consequence the method of titration advised by Cole, *vide* Cole and Onslow (1916), is one in which the actual H-ion concentration is estimated. This concentration is denoted by the symbol $p_{\text{H}} = \log_{10} (\text{H})$, (H) denoting the concentration per litre of the hydrogen-ions. Those who wish to go into the full mathematical details must consult Cole's original work on this subject. After a wide series of experiments, Cole and Lloyd came to the conclusion that the **optimum reaction or H-ion concentration** for the gonococcus was that in which the $p_{\text{H}} = 7.6$. In media which are poor in buffer content and growth hormones, such as Thalmann's agar, this reaction must be adjusted correctly, but when the growth hormones are present in abundance, as in media rich in serum or ascitic fluid, etc., conditions remain favourable for growth under a considerable range of reaction. When in addition the buffer content is high, growth can be obtained over a wide range of reaction. They state further that the optimum p_{H} varies with the strain and is, in fact, a characteristic of it. They consider it possible that the optimum p_{H} may vary with the nature of the medium. They point out also that the optimum p_{H} for rapid growth may not be the optimum for prolonged viability, and they noticed that the cocci tend to autolyse more quickly when the reaction is alkaline to what they consider to be the mean optimum. Furthermore, they state that a careful study of the effect of changes of reaction on the production of toxins and on antigenic values of vaccines might lead to valuable results.

With regard to the **influence of amino-acids**, Cole and Lloyd state that it is essential to a satisfactory medium to have a fair proportion of these substances present. They point out that bacteria cannot obtain nourishment direct from pure protein, or even from peptone, and that the value of peptone depends on the fact that it contains a small amount of amino-acids in the free state, but further growth is maintained on the amino-acids slowly liberated from the peptones and polypeptides by the action of the bacterial enzymes. In consequence they employ instead of peptone a substance rich in amino-acids, which they have called "*tryptamine*." This substance is prepared by digesting casein with a powerful tryptic ferment for several days. By adding this substance to ordinary nutrient agar, they were able to obtain satisfactory growths of the gonococcus. This medium they called "*tryptamine* agar."

The Effect of the Special Growth Hormones or "Vitamins."—The influence of these substances on the growth of the meningococcus was clearly demonstrated by Lloyd (1916) and by Flack (1916), and Cole and Lloyd found that they were also of great value with regard to the gonococcus. These growth hormones are present in blood, but they are removed from the blood when the latter is filtered through paper, evidently by the process of adsorption. Also when blood broth is heated, the hormones appear to be adsorbed on to the protein coagulum, only insignificant traces remaining in the fluid. When blood is added to a medium containing a colloid such as agar, it would seem that there is a distribution of the growth hormones between the agar and the blood colloids. They state that a single filter paper can remove practically all the growth hormones from an agar medium. They found that meat extract prepared in the ordinary way contained some material that increases the growth of the gonococcus, and this material is not appreciably removed from the fluid by filtration through paper. This substance in the tissue extract, however, seems to differ from the growth hormones in blood in that the former stimulates increased growth in well established colonies, whereas the latter favours more the initial development of the gonococcal colonies. Hence a good medium should contain both tissue extract and blood. They consider that these growth hormones may profoundly modify the attributes of many organisms. Some of their experiments appear to show that the red corpuscles contain much greater amounts of growth hormones than the serum itself.

Their tryptamine-blood-extract agar is prepared as follows :—

Tryptamine-Blood-Extract Agar ("T.B.E. Agar").

(i.) *The Pancreatic Extract.*—Fresh pig's pancreas is freed from fat, as far as possible, minced finely in a machine, and weighed. For every gramme of the mince is added 3 c.c. of 0.5 per cent hydrochloric acid (by weight). This can be prepared approximately by diluting 13.7 c.c. of pure concentrated hydrochloric acid (sp. gr. 1.16) to make 1000 c.c. with distilled water. The mixture is well stirred at intervals for 30 minutes. For every 100 c.c. of 0.5 per cent hydrochloric acid used there is now added 6.4 c.c. of 5 per cent caustic soda. This usually gives a reaction about $p_H = 4.7$, which results in a readily filterable mass.

The mixture is well stirred and filtered on a large folded filter. If the correct amount of acid has been added the filtrate is perfectly clear. It is shaken with a little toluol and the reaction made less acid by the cautious addition of 10 per cent caustic soda. The optimum reaction for the preservation of trypsin seems to be about $p_H = 5.5$. This can be obtained roughly by adding the alkali until a portion of about 3 c.c. gives only a faint reddish tinge with a few drops of a 0.02 per cent alcoholic solution of methyl red. It should be stored in a stoppered bottle in a cool, dark cupboard.

(ii.) *The Digestion of the Casein.*—To about $1\frac{1}{2}$ litres of water (distilled, if readily procurable) in a large vessel gradually add 200 grammes of the commercial casein known as "lait-proto, No. 6(2)," dusting it in and stirring well to avoid, as far as possible, the formation of lumps. Transfer to a Winchester quart, which has the 2000 c.c. level roughly marked on a label, by means of a funnel with a wide neck. Wash out the mixing vessel and the funnel with a jet of hot water, adding the washings to the main bulk. Make the volume up to 2 litres. Shake well to break up any lumps. As the amount of alkali in the casein is not quite constant it is advisable to test the reaction of small portions of the mixture with cresol red and with phenolphthalein. The optimum reaction for the tryptic digestion of casein is about $p_H = 8.1$, at which reaction cresol red gives a reddish violet colour and phenolphthalein remains colourless. Should cresol red give a yellowish colour it is necessary to add 10 per cent caustic soda in 5 c.c. portions to the bulk until the desired point is reached. The mixture must be well shaken after each addition of soda. If the original solution gives a reddish tinge with phenolphthalein it is not necessary to adjust the reaction by the addition of acid.

To the alkaline solution thus prepared add 120 c.c. of the pancreatic extract and 10 c.c. of toluol as a preservative. Stopper with a cork, shake thoroughly, and incubate at 38° to 40° C. Shake the bottle well the next day to break up any lumps that may still remain. Allow the digestion to proceed for 10 days, shaking occasionally to keep the fluid saturated with toluol,

a few c.c. more of which may be added if necessary. At the end of the digestion the mixture is transferred to a 3 litre flask, treated with 15 c.c. of concentrated hydrochloric acid diluted to 200 c.c. with water, shaken, steamed for 20 minutes, and filtered. To the filtrate 5 per cent caustic soda is added until the reaction is nearly neutral to litmus, but it is important that it should not be alkaline to this indicator. The fluid thus obtained is known as "stock tryptic broth" or "tryptamine."¹

(iii.) *Preparation of the Agar.*—To 1 volume of the above broth add 2 volumes of tap water, and, if necessary, render the mixture distinctly acid to litmus by the cautious addition of strong hydrochloric acid. Add agar (powdered or fibre) to make 2 per cent. Dissolve by steaming and filter according to the usual laboratory procedure. To every 500 c.c. of the agar at the temperature of 65° to 70° C. add 50 c.c. of defibrinated sheep's blood and one egg-white well beaten. The addition of the egg-white is found to assist in the subsequent formation of the clot and materially to improve the final yield. The mixture should be transferred to (Erlenmeyer) flasks, and must be steamed for 45 to 60 minutes. The best yield is obtained by steaming in volumes not greater than 1 litre. The bulk of the clot can be very rapidly removed by straining through a fine wire sieve, the clot being squeezed by a glass plate or clock glass. The final clearing is effected by straining through a mat of glass wool supported on a perforated filtering disc in an ordinary funnel, the whole being kept hot by means of a hot-water funnel. *On no account must filter paper or cotton-wool be employed.*

(iv.) *Adjustment of Reaction.*—The reaction is brought to a hydrogen-ion concentration of $p_H = 7.6$. The method adopted is that used by Cole and Onslow.²

The method is based on the fact that solutions with the same hydrogen-ion concentration give the same tone and intensity of colour with certain special indicators. As bacteriological media are generally coloured, allowance must be made for this by viewing the standard solution through a layer of the medium employed. It is important to keep the relative concentrations of the indicator in the standard and test solutions quite constant. The effect of dilution of bacteriological media on the hydrogen-ion concentration is relatively slight. The tubes used for the method must be of thin clear glass, of exactly the same diameter. The stand figured here is adapted to hold special test-tubes having an external diameter of five-eighths of an inch.³

In the method described the comparison is made with tubes containing phosphate solutions of p_H 7.5 and 7.7, it being desired to obtain a tint intermediate between these. If preferred a single tube containing a phosphate solution of p_H 7.6 can be employed. This is left to the choice of the worker, some preferring the single tube, whilst others find it easier to get between two limiting tubes.

The standard solutions required are best prepared by adding standard soda to a standard solution of acid potassium phosphate (KH_2PO_4).

0.2 M. *Acid Potassium Phosphate.*—Dissolve 27.231 grms. in distilled water and make up to 1 litre.

0.2 N. *Sodium Hydroxide.*—This can be prepared by diluting accurately standardised normal soda with four times its volume of distilled water. To get exact results the soda should be free from carbonate. This can be obtained by the method given by Clark and Lubs, but for this purpose the ordinary soda gives a sufficient approximation.

Standard Solution $p_H = 7.5$.—To 50 c.c. of the acid potassium phosphate add 41.2 c.c. of the 0.2 N. soda and dilute with distilled water to make 200 c.c.

Standard Solution $p_H = 7.6$.—To 50 c.c. of the acid potassium phosphate add 42.8 c.c. of the 0.2 N. soda and dilute with distilled water to make 200 c.c.

Standard Solution $p_H = 7.7$.—To 50 c.c. of the acid potassium phosphate add 44.2 c.c. of the 0.2 N. soda and dilute with distilled water to make 200 c.c.

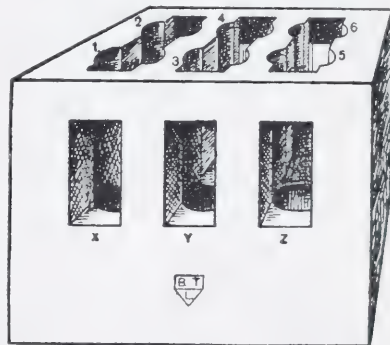


FIG. 2.—Stand to hold six test-tubes for colorimetric estimation.

¹ A concentrated solution of tryptamine can be obtained from Messrs. Baird & Tatlock (London).

² *Loc. cit.*

³ The colorimeter stand and special test tubes can be obtained from Messrs. Baird & Tatlock (London).

Indicator, 0.02 per cent solution of phenol-sulphone-phthalein ("phenol red"). This can be obtained in phials containing 2 c.c. of a 0.6 per cent solution, sufficient to prepare 60 c.c. of the dilute indicator required.¹

Into tube (1) measure 5 c.c. of phosphate solution. $p_H = 7.5$ and 0.5 c.c. of phenol red.

Into tube (5) measure 5 c.c. of phosphate solution. $p_H = 7.7$ and 0.5 c.c. of phenol red.

To tube (4) add about 5 c.c. of water.

Measure exactly 10 c.c. of the hot agar into 40 c.c. of cold distilled water and mix well. Before it has set measure 10 c.c. into tube (3) and add 1 c.c. of phenol red.

To tubes (2) and (6) add about 5 c.c. of the diluted agar.

Titrate the diluted agar in tube (3) with N/20 soda, preferably from a microburette, mixing well by closing with the thumb and inverting two or three times. If a microburette is not available the titration can be done by means of a 1 c.c. pipette graduated in 1/100ths c.c. Continue the addition of the soda until the colour tint seen by holding the box to the light and viewing through Y approaches that seen through X. Note the amount of soda used and add half this volume of distilled water to each of the tubes (1) and (5), the purpose being to keep the indicator at the same concentration. Continue to add the N/20 soda to tube (3) until the tint seen through Y is intermediate between those seen through X and Z, distilled water being added to tubes (1) and (5) as the titration proceeds. It is generally necessary to melt the agar at intervals by immersing the tube (3) in boiling water. It is of the utmost importance that the solution be well cooled before the colour comparison is made, as the tint is much affected by temperature variations.

The total amount of N/20 soda required for 10 c.c. of the 1 in 5 agar is read off. Twenty-five times this amount of normal soda is then added to each litre of the melted agar, and the whole well mixed.

The medium is now ready to be tubed and sterilised. It is probably better to do this by the intermittent method of steaming for 15 minutes on three successive days. For most purposes it can be done by steaming in the autoclave for 5 minutes, raising the pressure to 10 lbs. per square inch, *i.e.* obtaining a temperature of 115° C., and cutting off the heat as soon as this point is reached.

After sloping, the tubes must be incubated at 37° C. for 24 hours. If they are kept several days before inoculation, this preparatory incubation may be omitted.

The Preparation of Tryptamine-Spleen-Blood Agar.

Prepare tryptamine-blood-extract agar, as described above, except that 2.5 per cent agar is employed. Adjust the reaction to $p_H = 7.6$, as described in (iv.).

To 200 c.c. of this add 100 c.c. of the tryptamine-spleen-broth, also adjusted to $p_H = 7.6$. Tube and sterilise.

They state that in their experience it is good to allow the slope cultures to stand for two or three days at room temperature, or for 24 hours at 37° C. before use. This allows the surface of the agar to "mature," and better growths are obtained. They think that this may be due not so much to loss of moisture as to a gradual increase of the adsorbed hormones at the surface between the agar and the air.

With regard to the influence of such chemicals as salt, glucose, glycerol, and urea, they think that salt tends to be deleterious, though this effect is not very marked. They think that glucose has no influence on the initial growth and that it considerably shortens the viability of the cultures. One per cent glycerol they find is injurious when the reaction is adjusted to $p_H = 7.6$, but when more acid it may be beneficial. The influence of this substance seems therefore to vary with other factors in the medium. They found that 2 per cent urea was most distinctly deleterious to initial growth.

With regard to viability, Cole and Lloyd seem to have been the first to point out that very prolonged life can be obtained in stab cultures. Stab cultures on their tryptamine-blood-extract agar remain viable for four months or even longer.

¹ This and other valuable indicators are manufactured by the Cooper Laboratory of Economic Research, Watford.

The author considers that Cole and Lloyd have made a valuable addition to our knowledge of the cultivation of the gonococcus and of culture media in general. Their method of adjusting the reaction, which really originated with Clark and Lubs, is certainly an advance upon the older methods, and the method of prolonging the viability of the organism by the use of stâb cultures is very valuable.

The author has tested their various kinds of "tryptamine" agar and found that they grow the gonococcus satisfactorily. They seem, however, to possess one disadvantage, viz. that in the slope cultures the germs autolyse very rapidly, within 48 hours. This is also the chief fault of the tryptic-pea-extract agar used in the cultivation of the meningococcus.

Fluid Culture Media.—Most of the above-mentioned solid culture media have corresponding fluid extracts made in the same way, but not coagulated or solidified with agar. The remarks made regarding the various solid media can be applied more or less to the corresponding fluid media.

Thus corresponding to Wertheim's solid serum agar is a fluid serum bouillon consisting of two to three parts of meat-extract bouillon and one part of blood serum. This with ascitic, hydrocele, and pleuritic fluids, etc., may be considered as amongst the best and most suitable of all fluid culture media.

Similarly Von Wassermann's pig-serum-nutrose agar is represented in the fluid by pig-serum-nutrose bouillon.

Cole and Lloyd have fluid media, tryptamine-blood-extract broth, etc., corresponding to their solid media already described. These are prepared as follows:—

Tryptamine-Blood-Extract Broth ("T.B.E. Broth").

Dissolve 15 grms. of gelatin in 333 c.c. of tap water. Add 167 c.c. of tryptamine, 50 c.c. of defibrinated sheep's blood, and one egg-white, well beaten. Steam for an hour. Strain off the clot by means of a fine wire sieve, squeezing the clot well by means of a glass plate. Cool to 45° and measure. To every 100 c.c. add 2 c.c. of the pancreatic extract described in (i.), or of any other suitable tryptic preparation. Place the mixture in a tall cylinder and allow it to stand at room temperature over night. Siphon off the clear fluid, which must not be filtered through filter paper. The liquefaction of the gelatin can also be effected by incubation for two or three hours at 37° C., but the resultant broth obtained by this method is apt to be cloudy.

The medium must now be adjusted to $p_H = 7.6$. This is done in a manner similar to that described in (iv.), except that in tubes (2), (3), and (6) are measured 5 c.c. of the broth. To tube (3) is added 0.5 c.c. of phenol red. This is titrated with N/20 soda from a burette until the tint seen through Y is intermediate between that seen through X and Z. In this case the volume of water that has to be added to (1) and (5) is the same as the volume of soda employed.

For every 0.1 c.c. of N/20 alkali required for the 5 c.c. of broth, 0.1 c.c. of normal soda is added for 100 c.c. of broth. Sterilise by steaming or autoclaving as described above.

This medium is mainly used for testing fermentation reactions. Glucose, maltose, and sucrose are employed in 1 per cent concentration. The best indicator is phenol-sulphone-phthalein, 4 c.c. of a 0.06 per cent solution being added to every 100 c.c. of the sugar broth.

The Preparation of Tryptamine-Spleen Broth.

Remove the capsule from a bullock's spleen (milt). Mince the pulp and weigh. For every 100 grms. of pulp take 200 c.c. of water and 9 grms. of gelatin. Dissolve the gelatin in the water, cool to 40° C., and add it to the pulp. Incubate for two hours at 37° C. For every 1000 grms. of spleen pulp taken add 20 c.c. of defibrinated sheep's blood. Add also one egg-white for every 500 c.c. of the total mixture. Steam for an hour. Strain through a fine wire sieve. Cool to 45° C. and measure. To every 100 c.c. add 2 c.c. of one of the pancreatic extracts mentioned above. Place the mixture in a tall cylinder and allow to stand at room temperature over night. Siphon off the clear fluid, and measure. To every 100 c.c. add 50 c.c. of tryptamine broth. Adjust the reaction to $p_H = 7.6$ as described for the T.B.E. broth. Tube and sterilise by the intermittent method.

Those media which give the best results in the solid state are also likely to be the most satisfactory in the liquid form. As a general rule the solid culture media are best. They give profuse growths and yield a vaccine which is more or less free from the elements composing the medium. The viability on the solid slope cultures is as a rule not so prolonged as in fluid media, but this disadvantage is easily remedied by employing stab cultures. For some purposes, however, the fluid media are very useful. They are employed as a rule when we wish to estimate the sugar fermentation reaction of the organism. They are especially suitable for the cultivation of the gonococcus from the blood or from the serum or sero-purulent effusion of joints, etc. It is advisable to mix the blood or sero-purulent exudates directly with a certain amount (2 to 3 parts) of fluid agar at 40° C., and then to pour them into plates, or simply mix them with three times the amount of a suitable fluid medium. This dilution is advisable in order to lessen the bactericidal effect of the blood or exudate. Fluid culture media can only be used, of course, when the gonococcus is the only germ present, as is often the case in the blood or in the fluid of joints. In fluid media the gonococcus develops a slight acidity, especially when glucose is present.

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CHAPTER VI

RESEARCHES ON THE CULTIVATION OF THE GONOCOCCUS BY THE AUTHOR

RINGER'S SOLUTION — REACTION — HUMAN PLASMA — GLUCOSE — EFFECT OF HEATING —
FILTRATION — FURTHER EXPERIMENTS — FULL DETAILS IN PREPARATION OF AUTHOR'S
MEDIUM — COMPARATIVE RESULTS — AUTOLYSIS

TOWARDS the end of 1916 the author undertook the work of preparing gonococcal vaccine for the treatment of soldiers in the army. At that time the writer was not acquainted with the literature on the cultivation of the germ, and the media available in the laboratory for this purpose were tryptic-pea-extract agar and human blood agar containing the whole blood. The gonococcus could be isolated and subcultured on these media, but the growth was as a rule rather feeble. About 10 to 24 hours' slope cultures were generally required to produce 30 c.c. of an emulsion containing 1000 million gonococci per c.c. At the beginning of the year an output of about one litre of vaccine per month was sufficient, but after six months the demand had risen to about 10 litres per month. It became imperative, therefore, that a better culture medium should be devised in order to obtain more profuse growths. It appeared that these available culture media at the writer's disposal had the following defects :—

- (1) The growth was not sufficiently profuse.
- (2) The tryptic-pea-extract medium had a brownish-yellow tinge with a yellowish-coloured water of condensation, and in consequence yielded a straw-coloured emulsion.
- (3) The whole-blood agar was blackish-red and opaque, and had a brownish-coloured water of condensation containing a considerable amount of brown débris. The emulsions obtained from such slope cultures were tinted and contained débris in addition. These two defects made the vaccine difficult to standardise.
- (4) The tryptic-pea-extract agar did not appeal to the writer as being a natural culture medium. It seemed possible that on such a medium the gonococci might lose their virulence and antigenic power, by subculture, more rapidly than in the case of a medium containing blood.

Before the war the author had had considerable experience in the cultivation of protozoa and of human tissue *in vitro*; and, *vide* Thomson (1914), it was determined to apply this experience to the cultivation of the gonococcus. In the cultivation of tissue one employed unheated blood plasma, *i.e.* the whole blood minus the corpuscles, without the elimination of the clot or fibrin. In addition fresh unheated extract of tissue made up with Ringer's solution was necessary. In consequence the nutrient bouillon was made up with Ringer's solution instead of ordinary salt solution. This was compounded with Witte's peptone 1 per cent, and added to agar 2 per cent in the usual way. The nutrient agar was then filtered and titrated and made up to various reactions, *viz.* neutral, +6 acid, and +10 acid to phenolphthalein. These agars of varying reaction were then tubed (about 4 c.c. in each test-tube). After allowing the agar

to cool to about 50°C ., human blood plasma was added in varying amounts, $\frac{1}{2}$ c.c., 1 c.c., $1\frac{1}{2}$ c.c., and 2 c.c. The tubes were then sloped and allowed to solidify. The gonococci grew fairly well on all variations, but the growths appeared to be most satisfactory on those with a titration of +6 acid. The variation in the amount of plasma did not give widely different results. The growths appeared to be as profuse in the tubes containing $\frac{1}{2}$ c.c. and 1 c.c. as in those containing as much as $1\frac{1}{2}$ to 2 c.c. of plasma.

The addition of plasma rendered the agar too soft, so it was necessary to stiffen the medium by raising the agar to 2.5 per cent. Eventually it was raised still further to 3 per cent, as it was evident that the gonococcus grew better on a fairly hard surface. The growths on the soft 2 per cent agar plasma medium were certainly not good, and did not spread well over the surface. Attempts were made to stiffen this agar by placing the tubes in the incubator to dry the medium. After considerable drying for several days it was found that the gonococcus grew much more satisfactorily on the drier and harder surface, and moreover the growth spread better.

A fairly tough medium is more satisfactory all round for vaccine purposes, as the growth can be washed or rubbed off without tearing up the agar.

In the cultivation of the malarial parasite it is absolutely essential to add 0.5 per cent glucose to the human blood medium. This led the author to try the effect of adding glucose in the case of the gonococcus. Nutrient Ringer agar was prepared as before at the optimum reaction, +6 acid, and to this varying quantities of glucose were added, 0.5 per cent, 1 per cent, 2 per cent, 3 per cent, 4 per cent, and 5 per cent. Human plasma was added as before, $\frac{1}{2}$ to 1 c.c. to each tube.

The growths of gonococci were found to be more profuse than in the previous experiments, and the optimum amount of glucose was observed to be about 2 per cent or 3 per cent, and profuse growth was also obtained with as much as 5 per cent of this substance. The optimum medium therefore consisted of Ringer's solution, meat bouillon, 3 per cent agar, 1 per cent Witte's peptone, 2.5 per cent glucose, and to this was added $\frac{1}{2}$ to 1 c.c. of human plasma to each tube containing 4 c.c., *i.e.* a ratio of plasma to agar of 1 in 5 to 1 in 10.

This medium gave very excellent results, so much so that one usually obtained 30 c.c. of vaccine containing 1000 million gonococci per c.c. from one 24 hour slope culture, whereas with the former stock laboratory media it took as a rule some 10 slope cultures to produce this amount.

After some months' experience with this new medium it was noticed that different batches varied in their growing power, and it was difficult for some time to account for this. Eventually, however, the cause was very forcibly demonstrated as follows:—A litre of the medium was prepared in the usual way and filtered. The first portion of the filtrate that came through was tubed immediately and looked particularly white and clear. Owing to a shortage of test-tubes, however, the remainder was left in a flask. More tubes were obtained next day and filled from the re-melted contents of the flask. Sufficient tubes were again not available, so that the remaining contents of the flask had to be re-melted once again. It was now very markedly noticeable that the three batches of tubes varied in tint. The medium in the first batch was beautifully clear and straw-coloured. The second batch had a pale brown tint, while the third was darker brown in colour. It is well known that the longer bouillon agar is heated or koched the browner it becomes in tint. The writer has not, however, seen it stated that this heating destroys its properties as an efficient culture medium. The following observations will show that this is of the highest importance in the preparation of the medium. To all three batches of the same medium, fresh human plasma was added. The tubes which were pale straw in tint gave very profuse growths. The faintly brown tubes obtained after the second heating gave markedly inferior growths, while the deeply brown tubes from the third heating gave very poor growths. The relative merits of the three batches with regard to growing power as estimated by the yield of vaccine were as 1 to $\frac{1}{10}$ to $\frac{1}{15}$, so that by over-

heating of the bouillon agar alone one obtained growths only $\frac{1}{15}$ the strength in spite of the addition of fresh unheated human plasma.

After making this important observation the author determined further to improve the medium by turning out the Ringer-bouillon-glucose agar with the absolute minimum of heating, by increasing the speed of filtration, and by koching the end product only once for sterilisation purposes. Filtration through paper is too slow; through cotton-wool it is much more rapid and quite as efficient. Cole and Lloyd have pointed out that a filter paper removes by adsorption certain important properties necessary for growth, so the most satisfactory method of all would be to discard filtration altogether and to get rid of the turbid matter by sedimentation or by centrifugalisation. The quickest way would be to centrifugalise it, but a sufficiently large centrifugal receptacle was not available to enable this to be done. Most excellent results were obtained, however, by straining the molten medium through a silk handkerchief to remove the coarse sediment and allowing the filtrate to run into a tall cylindrical jar in the Koch steriliser. A towel was placed over the steriliser instead of the lid. This procedure prevented the temperature from reaching to boiling point, but it was still sufficiently hot to keep the agar molten and to allow sedimentation to take place. The supernatant clear bouillon agar was pipetted off from time to time and tubed, that which was tubed first with the least heating being always the least tinted and best.¹ From such the most powerful growths of the gonococcus were always obtained, the highest yield of vaccine being 150 c.c. of an emulsion of 1000 million gonococci per c.c. from one 24 hours' slope culture. Moreover, the emulsions obtained from such cultures were absolutely white in colour and very satisfactory to standardise. With such a clear medium one obtains a colourless water of condensation, and in consequence the vaccine is not tinted. Although the medium was now all that could be desired, still further improvements were attempted without being able to obtain any greater profusion of growth.

The following are, however, some further experiments which may be sufficiently interesting to record. Having been impressed by the destructive power of heat on the properties of the medium, the author determined to try the effect of using unheated extract. In the cultivation of tissue one employs fresh plasma plus fresh unheated extract of chick embryo tissue. The latter is obtained sterile by removing a seven-day-old chick embryo, aseptically, from the egg and mashing it up in sterile Ringer solution. It was decided also to use human urine instead of Ringer's solution, as it was possible that the former might contain substances very beneficial to the gonococcus. The following experimental media were prepared, and the results obtained are given opposite each variety:—

- (1) 4 c.c. urine agar + 1 c.c. extract of chick embryo + $\frac{1}{2}$ c.c. human plasma—feeble growth.
- (2) Same as (1) + 2.5 per cent glucose—copious growth.
- (3) Same as (1) + 2.5 per cent glucose and 1 per cent peptone—copious growth.
- (4) 4 c.c. urine glucose agar + 1 c.c. human plasma and no extract—little or no growth.
- (5) 4 c.c. urine glucose peptone agar + 1 c.c. human plasma and no extract—feeble growth.
- (6) 4 c.c. urine glucose agar + $\frac{1}{2}$ c.c. human plasma + $\frac{1}{2}$ c.c. chick extract—pretty good growth; autolysis in 2 days.
- (7) 4 c.c. urine glucose peptone agar + $\frac{1}{2}$ c.c. human plasma + $\frac{1}{2}$ c.c. chick extract—copious growth, discrete gonococci after 2 days.
- (8) 4 c.c. urine glucose agar (no peptone) + 1 c.c. chick extract and no plasma—no growth occurred.
- (9) 4 c.c. urine glucose peptone agar + 1 c.c. chick extract and no plasma—a fairly good growth which showed early autolysis and swelling in the gonococci.

¹ The author has recently discovered the cause of the browning of the culture medium due to heat. It is due to a chemical change which takes place in the agar when heated with acid or alkali. If agar is boiled with normal hydrochloric acid and then rendered alkaline with sodium hydroxide it becomes almost black in colour. This brownish-black substance, which is an indicator resembling turmeric, was found to be very deleterious to the growth of the gonococcus. Agar culture media should therefore be sterilised at neutrality ($p_n=7$).

With regard to the clearing of sediment from agar culture media a new method entirely has been adopted; see later.

Experiments 1 to 3 show the importance of glucose in obtaining a profuse growth of the gonococcus.

Experiments 4 to 6 show that tissue extract is necessary in addition to plasma in order to obtain a growth. Peptone can take the place of tissue extract to a slight extent only.

Experiment 7 seems to indicate that the addition of peptone to the tissue-extract-plasma medium helps to improve matters, as the gonococci did not autolyse so quickly.

Experiments 8 and 9 show that a medium containing tissue extract without plasma gives no growth, and that peptone can take the place of plasma to some extent.

These experiments proved that both plasma and tissue extract are necessary, and that glucose and peptone also help to improve the growing power of the medium. It did not appear that urine was any better than Ringer's solution. The fresh unheated extract of chick embryo was probably better than heated meat bouillon, but the difference was not so marked as to justify the use of a fresh unheated chick embryo extract, as the latter is very expensive and troublesome to prepare.

Further experiments showed that unheated human serum gave practically as good results as the human plasma. Very excellent growths were also obtained by substituting rabbit plasma for human plasma, and extremely copious growths were also obtained by using hydrocele fluid.

Some time after this the author became very interested in the literature on the subject, and determined to try the effect of using the sodium phosphate salt as recommended by Martin, instead of Ringer's solution. The growths obtained were quite as profuse as with the Ringer's solution medium, and moreover it was found that the gonococci did not autolyse so quickly, and hence the viability was prolonged. Repeated experiments showed that on this medium made up with the Ringer's salts the growth on slope cultures autolysed in about three days, whereas on the same medium made up with sodium phosphate no autolysis occurred until the sixth or ninth day. The latter salt appeared therefore to be distinctly superior to Ringer's solution.

Full Details for the Preparation of the Author's Culture Medium.—One of the most important points in the preparation of this medium is avoidance of prolonged heating in any of the stages where heating is necessary. In the preparation of meat bouillon the finely minced beef is usually heated with distilled water. Some workers, however, extract the beef by allowing the mince to soak for 24 hours in the distilled water in the ice-chest. This latter method ought to be better, and some experiments at present in progress seem to indicate that bouillon prepared in this manner is superior to that extracted by the heat. It is necessary, however, to heat the bouillon at some time to sterilise it, so we cannot so far use fresh unheated meat extract until some means of sterilising it without heat is devised. It may be possible to do this by shaking it up with chloroform and then allowing the chloroform to evaporate. For some time the writer used a beef extract prepared by heat as indicated below, and the results have been most satisfactory.

A.—Preparation of Double-strength Meat Extract.

Take a bullock's heart and cut away all the fat. Cut the heart into small cubes and mince them. Weigh the mince and place it in a pan with as many c.c. distilled water as there are grammes of heart. (2) Heat the mixture gently, stirring meanwhile with a glass rod until a temperature of 40° C. is reached. Keep at this temperature for 20 minutes. (3) Raise to boiling point and keep boiling for 10 minutes. (4) Strain through a perforated enamelled iron strainer and three or four thicknesses of butter muslin. (See Fig. 3.)

B.—Preparation of Disodium Hydrogen Phosphate Solution.

Dissolve 10.00 grammes disodium hydrogen phosphate (Na_2HPO_4) in one litre of sterile distilled water.

C.—Preparation of Nutrient Disodium Hydrogen Phosphate Bouillon.

(1) Measure the double-strength meat extract into a sterile flask and add to it an equal volume of the disodium hydrogen phosphate solution.

- (2) Weigh out as much good commercial peptone as will make a 1 per cent solution when mixed with the whole of the extract prepared as under (1). Take about a quarter of this extract, heat it to 60° C. and, in a mortar, mix it with the peptone so as to make a smooth paste.

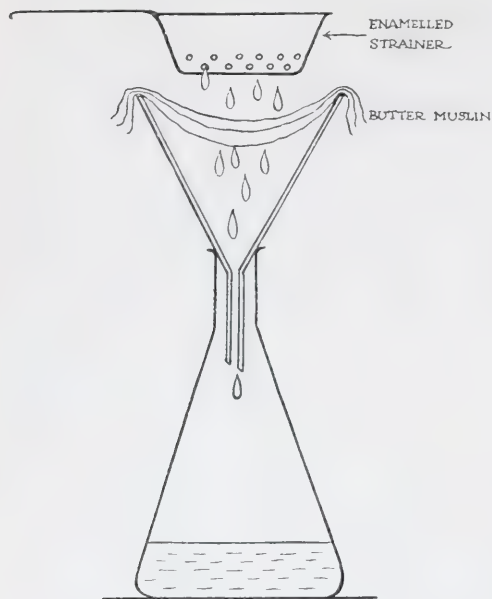


FIG. 3.—Straining of meat extract.

mixture to the remainder of the nutrient bouillon in the flask and steam in the Koch steamer until the agar is dissolved. This should occupy not more than 60 minutes in the case of powdered, and 90 minutes in the case of shredded agar.

- (2) Allow the agar to cool to 60° C., whip the white of one egg for every 300 c.c. of the agar solution, and add the froth to the latter. Replace in the steamer and steam for 30 minutes.

(3) Filter in the steamer through a layer of cotton-wool laid in a funnel, or outside the steamer through paper pulp laid on a Buchner funnel fitted into a vacuum flask (as shown in Fig. 4). Filtration should be as rapid as possible, as the medium deteriorates if it is kept long in the steamer.¹

- (4) Titrate carefully, using phenolphthalein as the indicator, and make the final product +6 acid

- (3) Add this emulsion to the extract in the flask and steam in the Koch steamer for 45 minutes, in order to complete the solution and stabilise its acidity.

- (4) It is advisable to add at this stage 10 c.c. of normal NaOH per litre in order to reduce the acidity as near as possible to the proper reaction.

The titration has to be carried out after the clarification and final filtration of the medium, and when much alkali is added a precipitate is formed; this is avoided by adding the bulk of the NaOH at this stage.

D.—Preparation of Nutrient Agar from the above.

Weigh out sufficient agar-agar to make, with the amount of nutrient bouillon prepared as above, a 3 per cent jelly. Mix this into a smooth paste with about one-third of the product of C (3), which must be cold. Add the

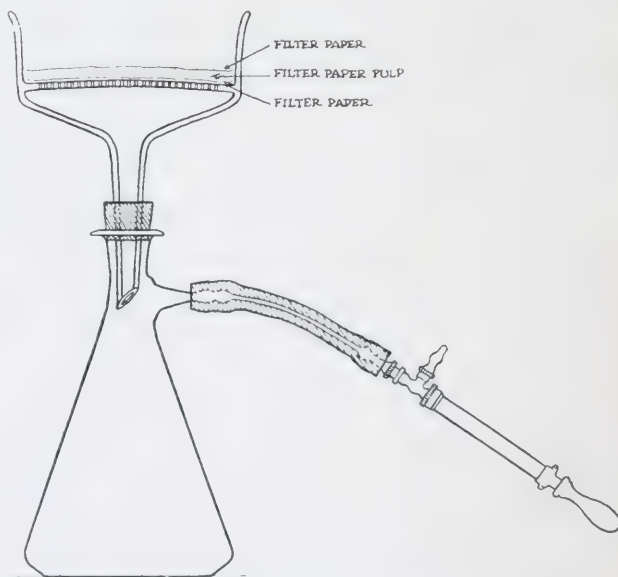


FIG. 4.—Method of filtering medium.

¹ The author's assistant, Mr. F. T. M. Downing, has recently experimented with the writer's sedimentation method, and has completely solved the problem. By his method of sedimentation in inverted flasks in a hot-air chamber the agar medium is completely cleared without the use of eggs and without the necessity of filtering at all. It is a very rapid method, and is a great advance in the art of preparing good culture media.

(Eyre's scale). Or better still, bring the hydrogen ion concentration to 7.3 to 7.6 p_H according to Cole's method.

(5) Add to the agar solution sufficient glucose powder to make of it a 2.5 per cent solution of glucose.

(6) Replace in the steamer and steam for 20 minutes. It is better to attempt sterilisation with one steaming than to steam on two or three successive days, and with care over the aseptic technique of the preceding steps this is usually successful.

(7) Tube the agar in sterile test-tubes, placing about 4 c.c. in each. Store the tubes of agar in the ice-chest.

E.—Addition of Human Plasma.

Provide the following :—

Apparatus for the drawing-off of blood from a vein into sterile test-tubes.

Sterile 10 c.c. centrifuge tubes, each containing 2 c.c. of a sterile 2.5 per cent solution of sodium citrate and plugged with cotton-wool.

Corks or rubber bungs in alcohol to fit the centrifuge tubes.

Sterile graduated 10 c.c. pipettes.

From any volunteer draw off about 20 c.c. of blood into a sterile test-tube and fill up centrifuge tubes at once with the freshly drawn blood. Cork the latter with one of the corks provided, having previously flamed off the alcohol, and spin in the centrifugal machine until the cells are deposited. Melt the required number of agar tubes, prepared as described above, in a water bath, and reduce their temperature to about 60° C. Pipette off the supernatant plasma in the centrifuge tubes and add 0.5 to 1.0 c.c. of it to each of the agar tubes. Mix the agar and plasma by rolling the tube between the hands, and slope in the usual manner. As a rule the yield from each centrifuge tube is about 6 c.c., or about enough for 10 tubes.

Incubate for 24 hours to make sure the medium is sterile.

The finished product should be a clear pale-straw transparent jelly, free from sediment. Any tinge of brown indicates overheating during the preparation.

The author has obtained very powerful growths by using instead of human plasma, rabbit plasma, hydrocele fluid from cases of gonococcal epididymitis, and fluid from gonococcal knee-joints.

Comparative Results.—At the request of Lieut.-Col. L. W. Harrison the author carried out a series of comparative tests with regard to the respective values of his own culture medium, Cole and Lloyd's tryptamine agar, and the tryptic-pea-extract agar used by Major Hine in the cultivation of the meningococcus.

Slope tubes of these media were inoculated as equally as possible from the same strain of gonococcus. After 24 hours' incubation the resulting growths were washed from the surface of each tube. The emulsions obtained were in each case standardised to 1000 million gonococci per c.c. and the yield in c.c.s. compared.

The results were as follows :—

Experiment 1.

- (1) Author's medium : one slope yielded 50 c.c. emulsion containing 1000 mils. per c.c.
- (2) Cole's tryptamine-blood-extract agar : one slope yielded 5 c.c. emulsion containing 1000 mils. per c.c.
- (3) Cole's tryptamine-blood-extract-spleen agar : one slope yielded 10 c.c. emulsion containing 1000 mils. per c.c.
- (4) Hine's tryptic-pea-extract agar : one slope yielded 10 c.c. emulsion containing 1000 mils. per c.c.

The yield from the author's human plasma glucose medium was therefore five times greater than the yield of any of the others. The sample of Cole's medium was old, however, and freshly prepared medium was obtained which was used in the subsequent experiments.

Experiment 2.

Two slopes of the author's medium yielded 160 c.c. (1000 mils. per c.c.).

Two slopes Cole's tryptamine-blood-extract agar	} yielded 75 c.c. (1000 mils. per c.c.) from the six slopes.
Two slopes Cole's tryptamine-blood-extract spleen	
Two slopes Cole's tryptamine-blood-extract lemco	

The average yield per slope was therefore six times greater in the case of the author's medium.

Experiment 3.

One slope of the author's medium yielded 70 c.c. (1000 mils. per c.c.).

One slope of Cole's tryptamine agar yielded 15 c.c. (1000 mils. per c.c.).

One slope of Cole's tryptamine-lemco agar yielded 10 c.c. (1000 mils. per c.c.).

The yield of the human plasma medium was therefore five times greater than that of the other two.

Experiment 4.

Two slopes of the author's medium yielded 153 c.c. (1000 mils. per c.c.)

One slope of Cole's tryptamine agar yielded 23 c.c. (1000 mils. per c.c.)

One slope of Cole's tryptamine-blood-extract agar yielded 12 c.c. (1000 mils. per c.c.)

One slope of Cole's tryptamine-lemco agar yielded 19 c.c. (1000 mils. per c.c.)

One slope of Hine's tryptic-pea-extract agar yielded 12 c.c. (1000 mils. per c.c.)

The average yield from the author's medium was in this case $3\frac{1}{2}$ times greater than the best of Cole's slopes and six times greater than the tryptic pea extract.

Experiment 5.

Two tubes of the author's human plasma-glucose agar were specially selected for their clearness and freedom from that brown tint indicating overheating, which experience has shown to militate against profuse growth.

They were inoculated as in the above experiments, and the yield obtained was 150 c.c. (1000 mils. per c.c.) and 90 c.c. (1000 mils. per c.c.) respectively.

The record yield from the writer's medium per slope is about 150 c.c. and the average is about 80 c.c. (1000 mils. per c.c.) per each 24 hours' slope culture.

Observations regarding Autolysis of the Gonococci on the above Media.—On the human plasma-glucose-Ringer agar hardly any autolysis of the gonococci can be noticed after 48 hours' growth (No. 5, Pl. II.), and as a rule it does not become visible until after 72 hours. When the sodium phosphate salt is used instead of the Ringer salts, then no autolysis is noted as a rule until 6 or 9 days' incubation.

With both Cole's and Hine's medium the process of autolysis sets in much more quickly. It shows definitely after 24 hours, and in 48 hours as a rule this lysis is well marked (see No. 6, Pl. II.).

Optimum Temperature and Viability of the Cultures.—Even on the best culture medium the gonococcus thrives only within a certain range of temperature. Under 30° C. there is no development, and growth ceases over 38.5° to 39° C. According to Jadassohn (1910) the organism dies after a few hours at 39° to 41° C. Broughton-Alcock (1915) found that his aberrant strain resisted a temperature of 45° for 1 hour, but died after $\frac{1}{2}$ hour at 50° C. Wertheim has repeatedly asserted that the gonococci grow well at a temperature over 40° C., but this statement has not been confirmed by other workers. The writer found that very profuse growths are obtained at 37° C., and most workers seem to agree that the optimum temperature for growth is from 36° to 37° C.

Previous to the work of Lumière and Chevrolier (1914), low temperatures were also considered fatal to the gonococcus, and it was believed that cultures died after an exposure of about 48 hours in the ice-chest. This, however, is not the case. The author found a

slope culture to be alive after 14 days in the ice-chest at 4°C ., and Lumière and Chevrotier found that they could withstand very much lower temperatures. Now that we possess better culture media the effect of temperatures of 40°C . to 41°C . should be further tested, when it may be found that they do not die at this temperature so readily as was previously imagined. Perhaps Wertheim's statements will be confirmed in that they will be found to grow well at a temperature of 40°C . and even at 41°C .

The viability or length of life of a culture seems to vary very much according to the kind of medium used. Many authors claim a long period of viability on their special medium. The writer has already stated, however, in his remarks on Lumière and Chevrotier's work, that prolonged viability may be due to slow growth, and that on extremely good media where the growth is very luxuriant, the viability on slope cultures may be quite short.

The gonococcus lives longer as a rule in fluid media than on surface slope cultures. The best mode, however, of keeping the germ alive for a long time is to make stab cultures on a good brand of solid medium. In such stabs very slow growth occurs along the track of the needle, no doubt due to the fact that the oxygen is largely excluded. The author has recovered the germs alive from such a stab on his medium after 80 days, by inserting a platinum loop along the track of the growth and smearing some of the material on a fresh slope of this medium.¹ Cole and Lloyd claim that stab cultures on their tryptic agar medium remain alive for 4 to 5 months or longer. Lumière and Chevrotier recommend exclusion of the air by means of a layer of oil. The writer is satisfied that the best means of maintaining a given stock culture alive for a long time is to make stab preparations.

Col. Harvey, R.A.M.C., states that slope cultures of *B. typhosus* can be kept alive almost indefinitely by hermetically sealing the end of the culture tube in the blow flame. The writer has not tried this method in the case of the gonococcus, but is inclined to believe that it may apply similarly to this organism, since no doubt the heating of the end of the test-tube expands the air and leaves a partial vacuum in the tube when it has cooled. Such a condition, according to Lumière and Chevrotier, is conducive to long viability. When subculturing strains of the gonococcus for the manufacture of stock vaccines or antigen, it is advisable to make stab cultures of each strain about once a month. If the slope cultures die or become accidentally contaminated, then one can always recover the strain from the stab which is kept, so to speak, in reserve.

Stab cultures, and in fact all culture tubes, should always be capped with rubber caps to prevent the medium from drying up.

Summary and Conclusions regarding the Cultivation of the Gonococcus.—(a) *The best kinds of Culture Media.*—From the evidence obtained the various media which have been devised for the growth of the gonococcus may be divided into three categories:—

- (1) Those which contain fresh unheated human blood, blood serum, or human serous exudates such as ascitic, pleuritic, hydrocele or cystic fluids.
- (2) Those containing fresh unheated animal blood or serum.
- (3) Those containing other albuminous substitutes fresh or artificially prepared.

There can be little doubt that the media belonging to category (1) are the best, more especially those which contain human blood or serum, since it is constant in composition. Those containing exudates (excepting hydrocele fluid) vary in their constituents and may sometimes prove disappointing. The next best types of media are those which contain fresh animal blood or serum, belonging to category (2). Finally, although many media containing other albuminous and artificially prepared substitutes and belonging to category (3) certainly give satisfactory results, yet on the whole they are inferior to those

¹ Capt. Wyler, R.A.M.C., has recently recovered the gonococcus alive from stab cultures on the author's medium after a period of eight months.

media in the two former categories.¹ Although Cole and Lloyd and other workers have studied the conditions necessary for the growth of the gonococcus very thoroughly, yet we are still a long way from finding a substitute for fresh human blood or serum upon which the gonococcus has been accustomed to live for thousands of years. It is most reasonable to suppose that the medium which will cause least alteration in the virulence and other physiological and chemical characters of the gonococcus, is that which approaches most closely to the composition of the human plasma and tissues. The author believes that we should always use when possible a medium belonging to category (1), more especially when it is desirable to maintain the original virulence and antigenic properties of the organism, as in the preparation of vaccines, etc.

(b) *The Blood*.—Some observers state that the whole blood containing the corpuscles is better than the serum, and Cole and Lloyd believe that the red corpuscles are much richer in growth hormones than the serum alone. The writer agrees with Martin, however, that the corpuscles are of little, if any, additional value to the serum with regard to the growth of the gonococcus. Moreover, the advantage of having a clear transparent medium, obtained by removing the corpuscles, certainly outbalances any disadvantage resulting from their omission. The author has been in the habit of using the plasma instead of the serum, as the former was much superior to the latter in the cultivation of tissue *in vitro*. There has not been noticed, however, any particular superiority of plasma over serum so far as the growth of the gonococcus is concerned, but as it is very easy to obtain plasma by the addition of a little sodium citrate, there is no reason why we should remove the fibrin by allowing the blood to clot.

With regard to quantity, there does not seem to be any good gained by adding more than 1 in 5 or 1 in 10 to the medium. Martin thinks that even in the case of human serum, larger amounts only tend to inhibit growth, due to certain bactericidal properties present. Gonococci autolyse fairly rapidly in human serum, and certain animal sera are very strongly bactericidal to this organism. Torrey noticed that fresh rabbit serum was often remarkably injurious to the gonococcus, and the writer has been able to confirm his statements. It is found, however, that if the rabbit serum is heated to kill the complement its bactericidal properties largely disappear. Some workers therefore recommend that all sera should be heated to a certain temperature before they are added to the medium. This preliminary heating, however, is hardly necessary, since the author's experiments have shown that nutrient agar, to which strongly bactericidal rabbit serum was added at a temperature just over the solidifying point of the agar, gave very profuse growths of the gonococcus. It is likely that the agar medium itself is anti-complementary and adsorbs all the complement from the serum which is added, and thereby removes its injurious properties. From the literature on the subject, however, it must be admitted that animal sera vary greatly with regard to their suitability, and even the serum of the same species of animal may vary. It would appear that the most suitable animal sera are those of the ox, horse, donkey, sheep, and pig, whereas the sera of the rabbit, dog, and cat may give indifferent results.

(c) *Extract of Tissue*.—This seems to be essential for the successful growth of the gonococcus, and it is certainly essential for the growth of tissue *in vitro*. There can be no doubt that the tissue extract should be as fresh as possible and should be heated as little as possible. One should even avoid passing it through a filter paper, since heat destroys and filtration removes certain useful and essential properties.

Commercial extracts such as Bovril, Oxo, Lemco, etc., are not so good as those freshly prepared in the laboratory. Fresh extract prepared from ordinary lean beef has given as good results in the author's medium as that prepared from ox heart.

The ideal extract would be one prepared from sterile chick embryos taken from the egg with aseptic precautions and mashed up in sterile solution, according to Carrel's

¹ The author has recently found that a carefully prepared testicular agar made by a modification of Hall's medium is almost as good as any of the culture media belonging to category 1.

technique in the cultivation of tissue. Such an extract being sterile from the commencement requires no heating whatsoever. This method of obtaining fresh sterile unheated tissue extract is, however, too expensive and impracticable for ordinary work. In the preparation of ordinary beef extract, the writer prefers the cold method of extraction by placing the finely minced material in distilled water and allowing it to extract in the ice-chest for 24 hours. The fluid portion is strained away from the solid, and then it is not heated further than is necessary to sterilise it. In the process of heating it loses a large amount of material, as can be seen from the flocculus which is thrown down, but this cannot be avoided, as sterilisation is necessary. At any rate the secret of cultivation is to remember that heat deteriorates the value of all the complex albuminous constituents in the medium.

(d) *Peptone*.—It will be noted that many of the culture media mentioned contain no peptone. Peptone is therefore not a vital necessity, but there can be little doubt but that its presence improves a culture medium. Many commercial varieties appear to be satisfactory, viz. Fairchild's, Witte's, and Chapoteaut's peptone, and also Difco. Most workers recommend about 1 per cent as the optimum amount. Cole claims that his tryptamine broth is superior to peptone, since it is much richer in amino-acids.

(e) *The Best Salts to use*.—Sodium chloride has been shown to be somewhat harmful. Ringer's solution is an improvement, since the calcium chloride appears to neutralise the toxic action of the sodium salt. For the gonococcus, however, the best salt would seem to be the acid sodium phosphate (NaH_2PO_4). The viability is prolonged when this salt is used, and autolysis does not set in so quickly. The phosphate, moreover, as already pointed out, renders the reaction of the medium more stable, since it is a "buffer" salt. The optimum quantity seems to be about 0.5 per cent.

(f) *Glucose and other Chemicals*.—Glucose is apparently conducive to luxuriant growth of the gonococcus. Cole considers that it reduces the viability of the organisms, but this is a natural consequence because of the profuseness of the growth. The optimum amount of glucose appears to be about 2 per cent to 3 per cent.

Glycerine seems to be of more doubtful value. Von Wassermann's medium contains 2 per cent to 3 per cent of glycerine. Gurd maintains that 5 per cent of this ingredient inhibits the growth of the gonococcus. Van Saun, however, used a veal agar culture medium containing 5 per cent glycerine with successful results, and Roos's medium contains about 2 per cent of this substance. Weil and Noiré used saccharose 0.35 per cent, and also urea 0.4 per cent, apparently with good results. Nutrose about 0.5 per cent has been used by Von Wassermann and Watabiki. Cole and Lloyd state that 1 per cent glycerine is harmful where the medium has a p_{H} = 7.6, but may be beneficial when more acid. They found 2 per cent urea to be distinctly deleterious to initial growth.

(g) *Percentage of Agar*.—Various amounts from 1.5 per cent to 3 per cent have been recommended. The writer prefers 3 per cent since it is the firmest and does not sag or twist in the slope tubes. Two per cent to 2.5 per cent just tends to be on the soft side after the addition of plasma or serum to the extent of 1 in 5 to 1 in 10. A soft agar which tears up in the process of smearing with a platinum loop is certainly an annoyance, and a hard surface is to be desired when washing off the growth for vaccine and other purposes. Apart from these mechanical advantages it seems that more profuse growths occur on a firm surface; at any rate the growth appears to spread more readily, and does not remain so localised as on a soft surface. When a hard firm agar is employed it is advisable to cap the tubes with india-rubber caps to prevent an excessive drying up of the medium.

(h) *Optimum Reaction and Best Mode of Titration*.—The proper reaction has been a great source of controversy in the past. Now, however, the majority of recent workers believe in a slightly acid or neutral medium. The author believes that the optimum reaction is +6 acid to phenolphthalein (Eyre's scale). This as a rule on the author's medium represents a p_{H} of about 7.3, which also corresponds to the p_{H} of the human blood. That this is about the most suitable reaction cannot reasonably be disputed. If

any one believes that an alkaline reaction is good for the gonococcus, let him note the effect of shaking up an emulsion of gonococci in an alkaline solution. Alkali dissolves the gonococci almost immediately, whereas a weak acid preserves them almost indefinitely and prevents autolysis. The same is true for the meningococcus. It may be accepted as proved that a faintly acid or neutral reaction is the most suitable for the gonococcus.

With regard to titration, the method of Clark and Lubs, and advocated by Cole, in which the hydrogen-ion concentration or p_H is estimated, is undoubtedly superior to the older methods.

(i) *Filtration*.—The best method of filtration is that which is most rapid, since this means that the medium is exposed to heat for a shorter time. Filtration through a fine paper is very slow and is apt to adsorb useful properties. A quick and more satisfactory method is to filter the medium through a layer of cotton-wool placed in a funnel. If a Buchner funnel with a vacuum flask is employed, the filtration is more rapid. It is sufficient to have the filtration apparatus in the Koch steriliser with the lid off, and if a vacuum flask is employed, the process may even be completed at room temperature, before the agar has had time to cool.

Downing's sedimentation method, however, as mentioned before, is vastly superior to any filtration process.

(j) *The Optimum Amount of Oxygen*.—Absence of oxygen certainly inhibits the growth of the gonococcus. At any rate the growth proceeds much more slowly. Under such conditions of slow growth, however, the viability is greatly prolonged. A scarcity of oxygen as in a stab culture or under a layer of oil is therefore the optimum for prolonged viability. For luxurious or rapid growth, Wherry and Oliver consider that an oxygen tension rather less than that of the air is best. This reduced tension is produced by enclosing a culture of *B. subtilis* within the tube containing the gonococcus culture. The gonococcus certainly grows very profusely under ordinary aerobic conditions, but, if we are to believe the latter observers, the optimum oxygen tension is lower than that existing in the normal atmosphere.

(k) *The Optimum Temperature*.—Practically all observers are agreed that the best temperature for the growth of the gonococcus is about normal blood heat, *i.e.* a temperature of about 36° to 37.5° C.

(l) *Viability and Autolysis*.—As a rule, when the gonococcus dies autolysis soon sets in, and when autolysis has occurred the organism is certainly dead. Conditions which prevent autolysis are therefore likely to be conducive to long viability of germ. Slow growth such as occurs in a stab preparation and a slightly acid medium are necessary for prolonged life in the culture tube.

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CHAPTER VII

THE CHARACTERISTIC APPEARANCE OF THE GONOCOCCUS ON SOLID AND IN LIQUID CULTURE MEDIA

NAKED-EYE APPEARANCE—LOW POWER EXAMINATION—APPEARANCE IN LIQUID
MEDIA—HIGH POWER EXAMINATION OF COLONIES AND SMEARS

Naked-Eye and Macroscopic Appearances on Solid and Liquid Media.—The macroscopic appearance of the growth of the gonococcus is fairly characteristic, but it varies considerably according to the medium employed, and according to the way in which the culture is inoculated. If the medium is infected by allowing a few drops of a weak emulsion of gonococci in saline to run over the surface, then the growth shows as a number of small separate and discrete colonies (No. 1, Pl. II.). These individual colonies gradually increase in size, and may attain a diameter of from 2-3 mm. on a good medium. In consequence, many of the colonies may coalesce to form a mass of growth. If the surface of the medium is inoculated with the growth of a previous culture by means of a platinum loop, then the new growth appears as a continuous sheet, no individual colonies being seen, as shown in photograph No. 2, Pl. II.

The naked-eye appearance of the separate colonies or of the continuous film of growth varies somewhat according to the nature of the medium, or at any rate it depends to some extent upon the density or profuseness of the growth. If the growth is very scanty it shows as a thin, whitish-translucent film. If very profuse and thick, then it begins to show a faint yellowish-grey tinge and is of course less translucent. The growth is somewhat slimy and viscous, and seldom or never granular or powdery. On certain media, such as Cole and Lloyd's tryptamine agar, this viscosity is very marked. The viscosity increases as the process of autolysis advances. On the author's medium, this viscosity is not so noticeable, and the growth is easily washed or rubbed off the surface of the agar. The medium shows no clouding, as occurs with many other organisms, such as staphylococci, etc., which produce a whitish opacity in the plasma agar. The masses of gonococcal growth are very easily emulsified when shaken up in saline with glass beads, and, moreover, this organism is exceedingly soluble in alkali. If masses of the growth be shaken up in normal NaOH they dissolve quickly like soap in water, and form a clear solution. This phenomenon is fully discussed in the next chapter on autolysis. The length of time required for the growth to become visible after inoculation depends upon several factors, such as the suitability of the medium and the amount and nature of the inoculation. A human plasma-glucose agar slope, if inoculated from a previous culture by means of a platinum loop, will show a distinct growth after 5 hours at 37° C., and the growth is very luxuriant after 24 hours. Under such circumstances the growth attains its maximum in about 24 to 30 hours, the whole surface of the agar being covered with a thick film. If, however, this medium is inoculated with pus containing very few gonococci, no growth may appear until the fourth day of incubation, and then only a few small white points. One should be careful therefore not to discard a culture made from pus as negative until

EXPLANATION OF PLATE II

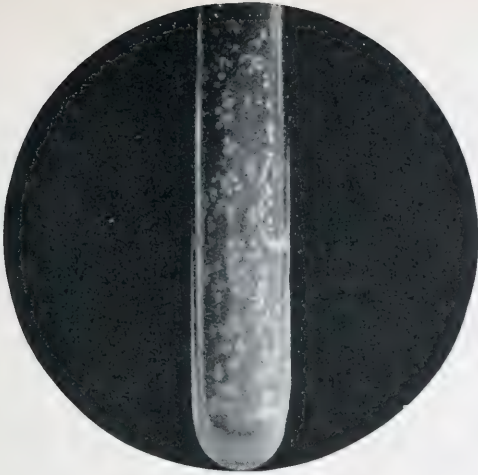
No. 1.—Culture of the gonococcus (24 hours' growth) on the author's glucose-plasma-agar medium. Shows discrete colonies. Natural size.

No. 2.—Same as No. 1, except that there is a continuous sheet of growth, the medium having been inoculated by rubbing it with a platinum loop. Natural size.

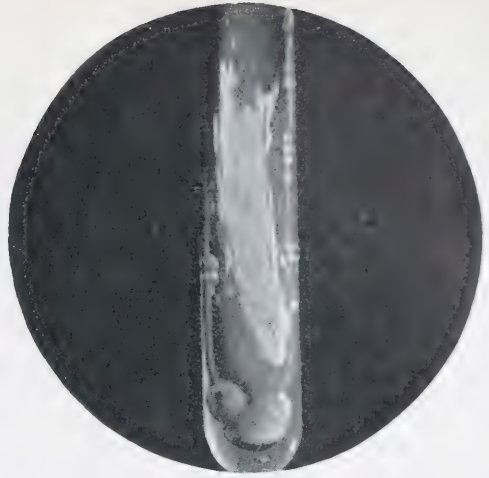
Nos. 3 and 4 are discrete colonies from No. 1, magnified about 30 diameters. Note the characteristic scalloped margins, the radial striations, and concentric rings.

No. 5.—Gonococci magnified 1000 diameters. Microphotograph of a stained smear from a 48 hours' culture on the author's glucose-plasma-agar medium. Note that the gonococci are discrete and show no signs of autolysis.

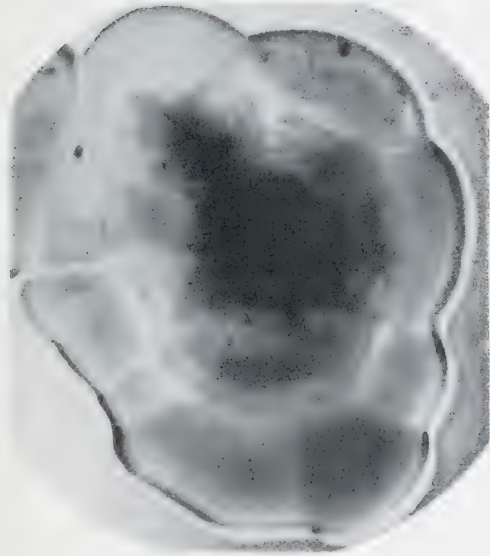
No. 6.—Gonococci magnified 1000 diameters. Microphotograph of a stained smear from a 24 hours' culture on Cole's medium. Note that the gonococci are very indistinct, having largely autolysed or disintegrated.



No. 1.



No. 2.



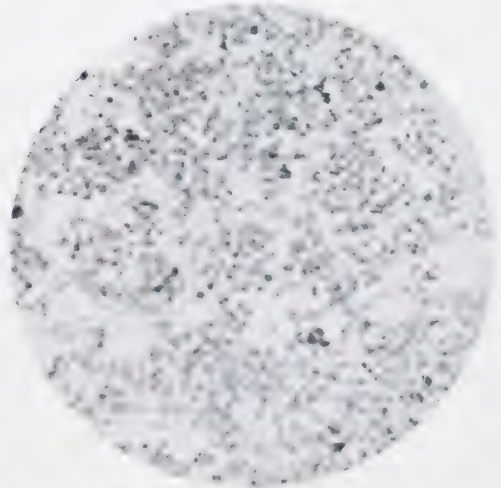
No. 3.



No. 4.



No. 5.



No. 6.

it has been incubated for 4, 5, or even 14 days. On one occasion the author inoculated his culture medium with pus from a gonorrhœal joint, and the first colonies of gonococci only appeared after 10 days' incubation. If the pus contains numerous gonococci, however, the colonies usually appear after 15 to 24 hours' incubation.

Jos. Koch states that on ascitic agar the first generation of the gonococcus colonies generally develop within the first 20 to 24 hours, but there are strains which develop colonies only after 48 hours. Jadassohn states that the growths of the colonies attain their maximum after 3 to 14 days. Generally speaking, they do not increase in size after the fourth or fifth day. Strains which have passed through several subcultures on artificial media such as ascitic agar generally develop large colonies. Koch states that the microscopic appearance of the cultures on ascitic agar is somewhat characteristic; as a rule after 24 hours at 37° C. the colonies measure about 1 mm. in diameter. If, however, the medium is dry, very insignificant or no growth may occur. The colonies appear circular after 24 hours, and are light grey blue in colour, opalescent, and somewhat iridescent. They are very mucilaginous in their consistence. When the medium has been inoculated profusely, the colonies become contiguous but do not coalesce, so that the culture has often a rippling or wavy appearance, which Kiefer describes as resembling crushed ice when held up to the light. With an exceptionally profuse growth the colonies may be fused to form a greyish-white film. Sholtz states that on ascitic agar the growth shows a soft transparent greyish colour in 24 hours. On horse-blood agar it forms a greyish-white film. As a rule on ascitic agar the separate colonies resemble those of the streptococcus and pneumococcus, but the gonococcus colony is nearly always larger, and has generally more colour, less transparency, and is much more adhesive and viscous in consistence.

Microscopic Appearance of the Colonies under the Low Power.—This has been studied very carefully by Martin and others. Under the low power the colonies show a light yellow to a yellowish-brown colour after 24 hours. In some cases they have an extraordinary mosaic layer-like construction, and at other times they show little excrescences on the surface and margins. The centre of the colony as a rule is raised and fluted, and the whole colony shows concentric as well as radial striations running out to the margin of the growth, which has nearly always a wavy or jagged edge. Martin describes the margin as being transparent and scalloped (see Nos. 3 and 4, Pl. II.). Colonies of 48 hours' growth on a moist medium usually reach a diametrical measurement of from 2 to 3 mm. The centre now shows a brownish colour, and the irregular scalloped margin is very distinct. In the middle of the colony there is often a crystal-like stratification, which has often been described in the case of other diplococci.

The Appearance of the Cultures in Liquid Media.—The liquid cultures, especially in ascitic bouillon, do not become diffusely opaque. The gonococci develop in the first place on the surface of the bouillon, and form there after 24 to 48 hours a fine granular layer of little grape-like masses. When shaken gently these sink to the bottom in the form of little flakes or crumbs. Further development ceases when this material falls to the bottom. In inoculating a liquid medium a copious supply of gonococci should be added. If a hanging drop from the liquid culture is examined under the microscope, the gonococci are seen in small or larger masses, and the individual diplococci are not easily distinguished. The germs show no sign of independent motility.

Appearance of Colonies and Smears under the High Powers of the Microscope.—If the larger colonies be squeezed out between a cover slip and slide, it will be noticed that the cocci in the centre of the colony are degenerating, which points to a very early death of the germs after luxurious growth. The degenerate forms are noticeable first on account of their swollen appearance, also they stain unequally, and when the disintegration is far advanced they appear as faintly stained granular masses in which no definite cocci are recognisable. At the edges of the colonies, on the other hand, the cocci stain well and show the definite coffee-bean shape. In stained smear preparations one gets a mixture

of the young typically-shaped diplococcal coffee-bean forms and the old degenerate swollen and granular types. This rapid degeneration of the cocci often begins after 20 to 24 hours' growth, but this depends upon many factors, such as the reaction and suitability of the medium, also upon the nature of the salts present and the rate of growth. According to Herzog (1902 and 1913), who studied the morphology and degeneration of the colonies very carefully, by staining them with Giemsa's stain 1 in 40 for one hour, those at the periphery and those in the centre are very different in appearance. Those at the periphery stain a deep blue violet colour, and show the typical coffee-bean shape, while those in the centre stain more feebly as a pale red violet, also the coffee-bean shape is absent, and the cocci are for the most part very small.

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CHAPTER VIII

THE CAUSE OF AUTOLYSIS OF THE GONOCOCCUS

PREVIOUS LITERATURE—THE AUTHOR'S RESEARCHES—FURTHER EXPERIMENTS AND TABLES OF RESULTS

IF one examines, microscopically, a smear prepared from a slope culture of the gonococcus during the first twenty-four hours' incubation, it will be found that all the gonococci are discrete (see Pl. II., No. 5). After twenty-four hours' incubation, however, on certain kinds of solid culture media (especially tryptic agar) it will be noted that nearly all the germs are autolysed into a mass of granules (see Pl. II., No. 6). Only a few diplococci remain, and these as a rule are greatly enlarged or swollen types. On an agar culture medium made up with Ringer's solution and containing fresh human plasma, the gonococci remain discrete and distinct for about three days. If sodium phosphate is used instead of Ringer's solution then the autolysis is still further delayed until the sixth or even the ninth day of incubation. If a fresh emulsion of gonococci from a twenty-four hours' culture is made up with normal salt solution and placed in the incubator at 37.5°C ., it can be noticed that they commence to autolyse in a few days. The meningococcus behaves in these respects similarly to the gonococcus.

Researches on Autolysis by various Observers.

The cause of autolysis in the meningococcus was studied very carefully by Flexner (1907). He concluded that the rapid autolysis and brief vitality of cultures of the meningococcus could not be ascribed directly to exhaustion of the culture medium or to the accumulation of injurious by-products of growth in the short period of 24 to 48 hours. He found, however, that 2 c.c. of a concentrated extract of autolysed meningococci, when added to 8 c.c. of the culture medium, inhibited the growth considerably.

With regard to saline emulsions of living meningococci, he noted that they died more quickly at 2°C . than at 37°C ., and they died more rapidly in dilute than in concentrated suspensions at 2°C . At 37°C ., however, concentration had the reverse effect, since they lived longer in weak than in concentrated suspensions. At 37°C ., therefore, the cocci died quickly in concentrated saline emulsions, and when death occurred they autolysed very rapidly, and their virulence towards guinea-pigs went off rapidly. In the ice-chest at 2°C . the cocci did not autolyse rapidly after their death, but remained discrete and preserved for a considerable time. When the meningococcus was suspended in Ringer's solution instead of ordinary salt solution he found that the viability was greatly prolonged. At 2°C . they survived for 8-10 days—three times as long as in the case of ordinary saline. At 37°C . they survived many days. Ordinary salt solution was therefore injurious to the meningococcus, but the toxic effect of the sodium chloride was neutralised by the calcium and potassium salts in the Ringer's solution. He found that the addition of a calcium salt to the culture medium greatly increased the period of viability of the meningococcus. On such a medium they did not autolyse nearly so rapidly as on a medium containing sodium chloride alone. Fischer (1900) showed that the passage of a micro-organism from weak to more highly concentrated salt solutions sometimes caused plasmolysis. Flexner states that the death and autolysis of the meningococcus is not

caused by hypertonicity of the medium alone, by starvation alone, by degree of concentration alone, or by a natural brief period of vitality. He says that the autolysis of the dead cocci is due to an intracellular enzyme existing within the meningococcus itself. This enzyme is less destructive in Ringer's solution suspensions as compared with its action in ordinary salt solution. He found that if a suspension of meningococci was heated to 60° C. for 30 minutes the cocci were killed, but the intracellular enzyme or lysin was not affected. Heating to 65° C. weakened the enzyme, and in consequence the autolysis was delayed. Heating to 70° C. for 30 minutes greatly reduced the power of the enzyme or lysin, but did not completely destroy it. Heating to 65° C. or upwards causes some plasmolysis or plasmoptysis of the cocci, but prevents further action by the lysin. Lysed cocci do not settle readily, but remain suspended a long time and form little sediment. Cocci which are not autolysed settle fairly quickly, and form a considerable sediment. Toluol when added to a saline emulsion of meningococci at 37° C. caused complete autolysis in 4 hours. Ringer's solution did not prevent this. Loeb (1906) showed that potassium cyanide restrained intracellular zymotic activity. Flexner found that this held good with the meningococcus, since a solution of $\frac{1}{250}$ per cent KCN inhibited autolysis. He observed that the meningococcus enzyme autolysed other organisms, and that it apparently autolysed the Gram-negative types more readily than the Gram-positive varieties. Non-autolysed meningococci were virulent to guinea-pigs, but with some strains the virulence deteriorated quickly by sub-culture on artificial media. Other strains retained their virulence for months on sheep-serum agar. Suspensions in sheep-serum water were more virulent than suspensions in saline. The virulence of suspensions deteriorated rapidly with keeping. Autolysed meningococci, filtered or centrifuged to get rid of the sediment, were also lethal to guinea-pigs. Heating the autolysate to 65° C. did not materially reduce its toxicity, so that the toxin is probably independent of the enzyme. Since the toxic action of the diplococcus was due to an endotoxin and depended on disintegration, reduction in the rapidity of dissolution might easily affect the results. Injections of living cocci were, however, more lethal than the dead organisms, probably because the former multiply for some time after the injection. At any rate he thinks this is more probable than the assumption that the toxin deteriorates quickly after the death of the coccus. The peritoneal exudate was more injurious to the meningococcus than the serum of the guinea-pigs. He thinks that the destroyed leucocytes yield to the exudate a substance injurious to the diplococci in that it brings them under the solvent action of their own enzyme. The peritoneal exudate of the injected guinea-pigs, however, also possessed solvent power in itself, as it dissolved cocci which had been heated to kill their own lysin.

Wollstein (1907) applied Flexner's experiments to the gonococcus and found that with regard to autolysis it behaved similarly to the meningococcus. She found that gonococcal emulsions at 37° C. in saline remained alive for 6 days, whereas in Ringer's solution they remained viable for 7 days. A concentrated suspension in saline was more viable than a weak one at 7° C., whereas at 37° C. the weak was more viable than the concentrated suspension. Ringer's solution, however, reversed this rule, so that weak suspensions were more viable at 7° C., and the concentrated suspensions were more viable at 37° C. Ringer's solution was not so superior to saline in prolonging viability in the gonococcus as was the case with the meningococcus.

On moist sheep-serum agar at 37° C. she found that the gonococcus was viable for 35 days, that is much longer than in the case of the meningococcus. At 7° C. the gonococcus was viable on sheep-serum agar for 7 days, about the same length of time as the meningococcus. She ascertained that the gonococcus autolytic enzyme was killed by heating to 65° C. for 30 minutes. Intraperitoneal injections of fresh living gonococcal emulsions prepared from recently isolated cultures were virulent to guinea-pigs and mice. After 17 to 18 generations by sub-culture this virulence decreased by more than one-half.

A suspension of a 24 hours' culture in 3 c.c. of saline + a few drops of toluol, when kept over-night at 37° C., was completely autolysed in the morning.

Torrey (1907) noted that, when an emulsion of gonococci in normal salt solution was shaken for a number of hours and then filtered, the resulting clear filtrate was decidedly toxic to guinea-pigs. It is almost universally agreed that the gonococcus does not produce an exotoxin, so that the toxic effect of the filtrate obtained by Torrey must be ascribed to endotoxin, liberated into the saline during the process of shaking, due to autolysis or disintegration of the gonococci.

McClintock and Clark (1909) carried out a number of experiments in order further to elucidate this phenomenon of autolysis in the gonococcus.

They noted that when gonococci were suspended in normal saline for 12 to 24 hours at room temperature, they lost their affinity for methylene blue; moreover, the emulsion began to lose in density, and the amount of deposit (when the cocci settled to the bottom of the tube) became gradually less in the course of time. A freshly prepared emulsion of the organisms took up the methylene blue stain readily, and they considered that the loss of staining capacity was due to autolysis. According to this staining test, therefore, autolysis occurred very rapidly in saline suspensions at room temperature. If, however, the suspensions were heated the autolysis was delayed or entirely inhibited. The addition of 4 per cent trikresol appeared further to defer the autolytic process. They concluded that permanent staining power, *i.e.* complete inhibition of autolysis, was secured by heating the original saline suspensions to 60° C. for 1 hour in the presence of 4 per cent trikresol, or by heating to 70° C. for 1 hour in the absence of trikresol.

The following table is reproduced from their paper on the subject:—

Stain, Methylene Blue.	Saline Suspension without Trikresol.			
	No Heat.	30° C. 1 hour.	60° C. 1 hour.	70° C. 1 hour.
Number of cocci staining after 24 hours .	None	Very few	None	Numerous
Number of cocci staining after 5 days .	None	None	Very few	Numerous

Stain, Methylene Blue.	Saline Suspension with 4 per cent, Trikresol.			
	No Heat.	50° C. 1 hour.	60° C. 1 hour	70° C. 1 hour.
Number of cocci staining after 24 hours .	None	Very few	Numerous	Numerous
Number of cocci staining after 5 days .	None	None	Numerous	Numerous

They also estimated the process of autolysis by staining and counting at intervals the number of cocci in a suspension. They noted that the counts became less and less as time elapsed. After half an hour at room temperature approximately 28 per cent of the cocci had lost the power to take up the stain. The suspension was then heated to 50° C. for 30 minutes, and a count made 22½ hours later showed that a further 38 per cent had lost their staining power. If a suspension was heated, however, to 70° C. for 30 minutes no decrease in the number of stained organisms could be detected. They further demonstrated this process of disintegration by a chemical test. A 24 hours' culture of gonococci was thoroughly washed and centrifugalised; the deposit of organisms was then suspended in saline for a time and filtered through a Berkefeld filter. This filtrate gave a precipitate with the addition of dilute acetic acid and heat, indicating the presence of some protein substance. If, however, the process of shaking up with saline, centrifugalising, decanting, and adding fresh salt solution was repeated several times, the filtrate eventually failed to give this test, indicating that no more protein was being liberated by the gonococci. The filtrates of saline suspensions left at room temperature for 6 to 24 hours gave a heavy precipitate with dilute acetic acid and heat. But if the suspension was first heated to 70° C. for half an hour, the filtrate did not give this reaction. They found that the addition of alcohol to saline suspensions prevented autolysis when the strength of the former amounted to 50 per cent and upwards. With lower dilutions, however, autolytic phenomena were still evident.

Stained specimens of autolysed gonococci showed numerous fragmentary cell membranes

still capable of taking the stain faintly, and indicated that the cell wall was not completely disintegrated. They consider that the autolysis of the gonococcus is brought about by rupture of the cell wall, with the consequent escape of the contents.

With regard to the effect of the gonococcal autolysate on the growth of the living germs, they found that it was inhibited. Ascitic-agar impregnated with the autolysate gave growths only half as profuse as those obtained on the same medium without it. With Thalmann's agar the presence of the autolysate inhibited the growth completely.

Warden (1915), after experimenting with various modifications of culture media, considered that least autolysis was obtained when the reaction was neutral. He states that the lysis is not caused by the amount or character of the nitrogenous elements in the medium, nor does it depend on the amount of oxygen. Variations in the temperature, within the limits of the viability of the gonococcus, did not alter the rate of lysis in the culture tubes.

He believed that the autolysis of the cocci was due to the presence of water, since he found that they were made more viable on a very dry culture medium.

He maintains that autolysis is an invariable character of the gonococcus in the presence of excess of water, and that it is due, probably, not to enzyme activity, but to water hydrolysis or solution. Autolysis, he says, begins with œdema of the coccus, and this is followed by the liberation of protein or protein split products, compounds containing phosphorus and fats.

The gonococcus protein, comprising 75 per cent of the entity of the organism, is liberated into the water or salt solution during autolysis, and at first exists in chemical forms representing the sum of metabolic activity at the moment of liberation. This complex protein undergoes fairly rapid changes in character, either by water hydrolysis or by the action of ferments not killed by high temperature or other agencies, so that in a short time the organic nitrogen has largely lost its identity as gonococcus protein and has assumed simpler chemical forms. The fats of the gonococcus obtained as fatty acids, neutral fats, or lipoids are of large bulk, and a considerable portion of the former are volatile and soluble in water and salt solution.

He states that suspensions of gonococci in water or in salt solution, as in the preparation of antigen and vaccines, undergo rapid, almost immediate autolysis, accompanied by the changes above mentioned, at all temperatures below the coagulation point of protein. Heat at 60° C. hastens the process, while heat at 70° C. coagulates the protein.

The lysis depends on the concentration of the suspension, and on the ionic content of the solution. In salt solution it occurs in all strengths. Sodium fluoride checks the lysis in about 10 per cent solutions. Calcium chloride causes compact flocculation of the cocci and delays autolysis. The hydrosol colloids permit lysis apparently in direct proportion to the available water. Suspension colloids such as serum (normal, immune, or inactivated) and lecithin water favour lysis. Weak solutions of the alkali oleates do not prevent lysis, but strong solutions prevent it. Dehydrating substances such as 50-95 per cent alcohol, 20-50 per cent acetone, and strong solutions of sugar (syrup) prevent lysis. Fatty substances, neutral fat, olive oil, lanolin, vaseline, and all other anhydrous substances more or less free from water, prevent lysis. Glycerine 75-100 per cent prevented lysis, and preserved the gonococci best of all the substances he examined. In this substance they remained unchanged for months. Lysis occurred, however, in 50 per cent glycerine.

In his conclusions he states that the autolysis of the gonococcus in water and in salt solution is probably due not to the activity of enzymes, but to other causes, among which water permeability and solution of fatty substances play important parts, and the lysis is probably initiated by excess of water.

The author is inclined to believe that Warden's conclusions are partly erroneous, since every writer in the literature on the cultivation of the gonococcus, with the single exception of himself, emphasises the importance of maintaining the cultures moist, if a prolonged viability is desired. It is a fact also that the most luxuriant growth is always to be found just above the condensation fluid (Cole and Lloyd, 1917).

Torrey maintains that the gonococcus is more viable in liquid than in solid media, since ascitic broth cultures remained alive for 5 or 6 weeks. This is in direct contradiction to Warden's statements.

Wollstein states that cultures on moist sheep-serum agar may remain viable for 35 days.

Again, suspensions of gonococci in water and saline certainly do not autolyse so rapidly as Warden would lead us to believe, and at lower temperatures in the ice-chest they only autolyse very slowly.

If the process of lysis were chiefly due to hydrolysis one would hardly expect this process to be inhibited by a $\frac{1}{500}$ per cent solution of KCN as noted by Flexner, nor is it likely that the process would be so markedly delayed in the ice-chest. Warden himself admits that the existence of enzyme in the live cocci is well known. He says that one is proteolytic, acting best in a slightly alkaline medium, and destroyed at 56° C. If the enzymes are completely destroyed at this temperature, then one is bound to admit that the lysis is not due to them, since Flexner found that this lysis was not affected by heating the cocci to 60° C. for 30 minutes. Is Warden, however, quite certain that the enzyme is actually killed at 56° C.? The author was at first more inclined to favour Flexner's view that the autolysis is due to the action of the enzyme on the coccus when it had died. After the coccus has been disintegrated by its own enzyme, then no doubt the products of digestion are dissolved by the watery medium, and further disintegration may, no doubt, occur by hydrolysis. Warden has scarcely sufficient evidence to show that the process is due more to the effects of the water than to the enzyme.

Later Warden (1917) published an article on the physico-chemistry of the gonococcus. He regards the gonococcus as a cell composed of substances in a colloid state, having an extremely soft delicate body and limiting surface, extraordinarily sensitive to changes of osmotic pressure and surface tension. The gonococcus, he states, contains various chemical substances which constitute an entity conformable to other cells of the animal type. There is little or no unsaponifiable matter like phytosterol or other higher alcohols, such as are found in large amounts in certain other micro-organisms, notably the tubercle bacillus. He regards the gonococcus as a cell, the content of which is homogeneous with the surface membrane even though the latter may preponderate in fatty constituents. The surface membrane is semi-permeable, that is, permeable to water under certain conditions, but probably impermeable to most colloids, including its own. The conditions which regulate the permeability are for the most part due to the influence of electrolytes, the surface tension and osmotic pressure. He considers that the interior of the gonococcus is a colloidal aggregate in a watery dispersion means, whereas the limiting membrane consists of colloidal particles of water in an oily dispersion means. Anions such as sodium hydroxide increase the permeability of the cells. Sodium chloride also acts as an anion. These anions promote the formation of emulsions of oil in water, such as he conceives to exist in the interior of the gonococcus cell. On the other hand, cations such as calcium decrease the permeability of the cell, and tend to promote the formation of water in oil suspensions, such as he believes to exist in the surface film of the gonococcus, and so they are protected. Isotonic mixtures such as Ringer's solution, particularly if containing a little protective colloid, such as gelatin or agar, exert no immediate change in permeability and tend to preserve the cocci. Alcohol, ether and chloroform, exert solvent power for fat in higher concentration; in low concentrations they act like calcium ions, producing agglutinative and protective effects. The sodium or potassium salts of oleic acids are fatal to the gonococcus, causing lysis in dilutions of 1 in 5000.

An interesting development of recent bacteriology is the discovery of a transmissible lytic agent for bacteria; this substance appears to be present in the intestinal contents of living beings, is able to pass through a porcelain filter, and when added to cultures of various organisms has the property of dissolving them.

This principle, known as d'Herelle's phenomenon (1917), is considered by him to be due to an ultra-microscopic organism which he calls a "bacteriophage."

A similar substance has been described by Twort (1915), who believes it to be of the nature of a lytic enzyme. The former is most active towards organisms of the coli typhoid group and the latter chiefly affecting staphylococci. The author is unable to find a record of its action against the gonococcus. Its nature has not yet been determined definitely, but it would seem from the evidence available to be due to an enzyme produced by bacteria.

A full review of the literature appears in vol. 6, No. 4, of the *Abstracts of Bacteriology*.

Investigations by the Author.—This investigation was carried out in order to ascertain the best mode of preventing autolysis from occurring in vaccines. It seemed reasonable to suppose that the vaccine might deteriorate very rapidly as the process of disintegration of the germs advanced. This process, as has already been shown, can be arrested by heating the suspensions of the organism to 70°C . for half an hour. Flexner, however, states that heating to 65°C . or upwards causes some plasmolysis of the meningococci, and the same is likely to occur in the case of the gonococcus. Heating, therefore, though it retards autolysis, might act otherwise injuriously upon the vaccine by altering the complex protein structure of the germs, and may therein destroy their antigenic power when employed therapeutically. Since the gonococcus dies rapidly in weak antiseptics such as 0.5 per cent carbolic acid, the author had been in the habit of making up the vaccine in normal saline + 0.5 per cent carbolic without any heating, and it was found that the cocci remained discrete in this suspension medium for 3 months and upwards when stored in the ice-chest. At incubator temperature 37.5°C ., however, they autolysed much more rapidly. Attempts were made to elucidate this problem for the sake of finding out some method of preparing natural unheated vaccines which would keep for a much longer time. Vaccine was made up in Ringer's solution containing 0.3 per cent trikresol, and this appeared to delay the process of autolysis, but only slightly. A little sodium bicarbonate was then added to the Ringer's solution, but this markedly accelerated the autolytic process, thereby rendering the Ringer's solution more unsuitable than the saline carbolic medium. It did not occur to the author at that time that a faintly acid vaccine should be tested. Later, however, some experiments were carried out for diagnostic reasons, to determine how long gonococci could be detected in urine, and this led to the discovery that weak acid almost completely inhibited autolysis.

Stein (quoted in Jadassohn's *Handbuch der Geschlechtskrankheiten*, vol. i.) maintained that the gonococcus can be cultivated from non-albuminous urine after 7 hours, but not after it had stood for 9 hours. If the urine is albuminous, however, they can be cultivated from it after 12 hours. He states that the organism cannot be demonstrated microscopically in concentrated urine after standing for 2 hours. He further maintains that urine has bactericidal and precipitating properties, and that after 8 hours the cocci lose their staining capacity in this medium.

In order to investigate this matter further an emulsion of gonococci was made up with urine which had been previously sterilised by boiling. This urine was found to react distinctly acid to litmus. The suspension of gonococci in the sterile acid urine was then placed in the incubator at 37.5°C . It was found that the organisms remained discrete for about 3 weeks; after that time some autolysis was noticed, but even after 48 days many were still discrete. This was a distinct surprise after Stein's statements, since it showed that autolysis was delayed very much longer in acid urine than in normal saline or Ringer's solution. After this it seemed that the whole secret of autolysis might be the reaction of the medium, alkali favouring autolysis and acid retarding it. It was subsequently proved beyond any doubt that this view was correct. A suspension of gonococci in sterile urine, which had been rendered faintly alkaline with weak sodium hydroxide solution, and a similar suspension in the same urine, rendered faintly acid with acetic acid, were placed in the incubator at 37.5°C . In the alkaline urine suspension marked autolysis was observed after 24 hours and was practically complete in two days, whereas in the acid urine suspension the majority of the gonococci were still discrete after 28 days. A very beautiful demonstration of the importance of the reaction can be carried out by making suspensions of gonococci in solutions of the three sodium phosphate salts (the strength of these phosphate salt solutions which the writer used was 0.6 per cent in distilled water). In the Trisodium phosphate (Na_3PO_4) suspension, which is markedly alkaline, complete autolysis occurred at 37.5°C . in 24 hours. In the Disodium hydrogen phosphate (Na_2HPO_4) suspension, which is faintly

alkaline, complete autolysis occurred at 37.5°C . in 2 days, whereas in the sodium dihydrogen phosphate (NaH_2PO_4) suspension, which is definitely acid, practically no autolysis was observed at 37.5°C . till after 20 days had elapsed. The difference in the three suspensions was noticeable macroscopically as well as microscopically. In the two alkaline phosphate suspensions after two days, very little sediment of cocci appeared at the bottom of the tubes on standing, and the fluid above was faintly opalescent, whereas with the acid phosphate suspension a heavy deposit of gonococci was found at the bottom of the tube and the fluid above was perfectly clear, indicating that no autolysis had occurred. In all experiments, however, the microscopic test was employed. The tube is well shaken up and a loopful of the suspension smeared on a glass slide. This is dried and fixed by heat, and then stained by Gram's method. On microscopic examination of this stained specimen one can readily determine whether or not the gonococci have dissolved or autolysed. As it would appear proved that this autolysis is largely a question of reaction, the intracellular enzyme discovered by Flexner in the meningococcus, and similarly demonstrated by Wollstein in the gonococcus, must be of the nature of a tryptic ferment, since it can only act in an alkaline and not in an acid medium.¹ If we return now to reconsider Stein's statements on the viability and the length of time that gonococci can be demonstrated microscopically in urine, it is quite evident that this depends largely upon the reaction of the urine. It is well known that septic urine is alkaline and that any urine exposed to outside organisms will rapidly become alkaline on standing, due to bacterial decomposition. In such circumstances there can be little doubt that the gonococci would die quickly and autolyse rapidly, so that Stein's individual observations may have been quite correct. On the other hand, if the urine is acid and drawn off aseptically into a sterile vessel, it is conceivable that any gonococci present might be demonstrated microscopically for many days. Flexner showed that the process of autolysis was much slower in the ice-chest at 2°C . than in the incubator at 37.5°C ., due doubtless to the fact that the intracellular enzyme acts much more strongly at blood heat than at lower temperatures. This retardation of autolysis at low temperatures is also very noticeable in the case of the gonococcus. For example, an emulsion of gonococci in 0.6 per cent saline showed little signs of autolysis after 3 months at about 2°C . in the ice-chest, whereas at incubator temperature 37.5°C . autolysis in this solution may be quite marked in about 7 days.² There can be little doubt that the process takes place at least ten times more rapidly in the incubator than in the ice-chest.

At room temperature the rate of autolysis will be somewhat between the two. In the case of gonococcal vaccines made up to a strength of 1000 million cocci per c.c. in 0.6 per cent saline + 0.5 per cent carbolic acid and in 0.6 per cent Ringer's solution + 0.3 per cent trikresol and left constantly in the ice-chest, gonococci were found microscopically after 4 to 6 months had elapsed. It was nevertheless evident that a considerable change had occurred in the vaccine, since many of the cocci had become swollen, and some had actually autolysed into a granular debris. Similar suspensions placed in the incubator at 37.5°C ., showed as a rule marked signs of autolysis within a week, indicating that the process of dissolution was twenty times more rapid at the latter temperature. This would seem to be of great importance with regard to the preparation and storage of vaccines.

Further Experiments and Tables of Results.—It occurred to the author that the gonococci might not break up and lose their discrete shape so rapidly from autolysis if put up in a more or less solid, gelatinous, or oily medium. This view proved apparently to be correct. A concentrated suspension of the germs in 0.6 per cent saline (NaCl) was added to an equal quantity of molten 10 per cent gelatin³ at 37.5°C ., and placed in the

¹ More recent researches by the author appear to show that very weak solutions of alkali can dissolve the proteins of germs without the aid of any enzyme, and that the solvent power of the alkali is more potent at high than at low temperatures.

² Different strains of gonococci seem to autolyse at different rates.

³ The reaction of the gelatin was distinctly acid, and this may have accounted entirely for the delayed autolysis.

incubator. Samples of this molten gelatinous suspension were examined microscopically at intervals, and it was found that autolysis took place more slowly than with the saline alone, and many discrete cocci were found after a lapse of 26 days.

Two similar saline gelatinous suspensions were made, but containing in addition 1 drop of iodine (Lugol) solution and 1 drop of 3 per cent basic fuchsin per c.c. respectively. In these the autolysis was still further delayed, discrete cocci being found after a lapse of 41 days at 37.5° C. This would seem to show that certain chemical substances retard the action of the autolytic enzyme, as already noted by Flexner in the case of KCN and by McClintock and Clark with 4 per cent trikresol. No appreciable delay in the process was noted, however, with the addition of 0.5 per cent carbolic or 0.3 per cent trikresol, and in the case of iodine it would appear that dilute solutions delay autolysis, whereas strong solutions cause the cocci to break up more quickly. This, of course, is what one would expect to happen. Any strong chemical, acid for example, would quickly break up the cocci, whereas very weak acid would delay autolysis, but it would be very wrong to interpret the former by saying that it favoured the action of this autolytic ferment. In each experiment, therefore, we must not confuse the process of autolytic dissolution with that of chemical disintegration. Though it would appear, therefore, correct to conclude that weak iodine hinders the action of the autolytic ferment, we cannot equally conclude that the stronger iodine favours its action.

Gonococci suspended in gelatin and tragacanth and kept in the ice-chest appeared to remain discrete almost indefinitely. Why this should be so is difficult to explain; perhaps it depends on factors belonging to the domain of colloid chemistry.

The following tables show the results of the various experiments carried out:—

TABLE I
SUSPENSION OF GONOCOCCI KEPT IN THE INCUBATOR AT 37.5° C.

Time.	0.05% NaCl.	Ringer's Solution.	Ringer's Solution : 0.03% Sod. Bicarb.	Ringer + 0.03% Sod. Bikarb. : 0.3% Trikresol.	Distilled Water.	Distilled Water : Weak Acetic Acid.
1 day	Sometimes autolysis slight	Slight autolysis	Considerable autolysis	Marked autolysis	Little autolysis	No autolysis, but some swelling of the gonococci
2 days	Sometimes marked autolysis	"	"	"		
3 days	Little autolysis with some strains	"	"			
5 days	Marked autolysis with others	Considerable autolysis	Marked autolysis	Complete autolysis	Marked autolysis	Gonococci swollen but not autolysed
7 days	"	"	Complete autolysis			
14 days	"	Marked autolysis			Complete autolysis	
19 days	Complete autolysis					

TABLE II

SUSPENSION OF GONOCOCCI KEPT IN THE INCUBATOR AT 37.5° C.

Time.	Sterile Urine Naturally Acid.	Sterile Urine : Weak Acetic Acid.	Sterile Urine : Weak NaOH.	Sodium Phosphate (0.6%) Na ₂ PO ₄ Alkaline.	NaH ₂ PO ₄ (0.6%) Slightly Alkaline.	NaH ₂ PO ₄ (0.6%) Acid.
1 day	No autolysis	No autolysis	Marked autolysis	Complete autolysis	Almost complete autolysis	No autolysis
2 days	"	"	"	"	Complete autolysis	No autolysis
3 days	"	"	Almost complete autolysis			"
7 days	"	"	Complete autolysis			"
14 days	Slight autolysis	Some autolysis, but majority discrete				All discrete
19 days	Marked autolysis, but not complete	Majority discrete				Practically all are discrete
27 days		Majority discrete				Some autolysis, but majority discrete
34 days	Autolysis not yet complete					"
40 days	Still a few discrete gonococci					Majority still discrete
48 days	"					"
60 days	Autolysis nearly complete					"

TABLE III
SUSPENSION OF GONOCOCCI KEPT IN THE INCUBATOR AT 37.5° C.

Time.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.	NaH ₂ PO ₄ (0.6%) + 1.0% Iodine.
1 day	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis
2 days	"	"	"	"	"	"	"	"	"
3 days	"	"	"	"	"	"	"	"	"
5 days	"	"	"	"	"	"	"	"	"
7 days	"	"	"	"	"	"	"	"	"
14 days	"	"	"	"	"	"	"	"	"
21 days	"	"	"	"	"	"	"	"	"
40 days	"	"	"	"	"	"	"	"	"
50 days	"	"	"	"	"	"	"	"	"

Iodine in first five columns was obtained from the tincture.

* Obtained from Lugol's solution.

TABLE IV
SUSPENSION OF GONOCOCCI KEPT IN THE INCUBATOR AT 37.5° C.

Time.	NaH ₂ PO ₄ (0.1%)	NaH ₂ PO ₄ (0.3%)	NaH ₂ PO ₄ (1%)	NaH ₂ PO ₄ (2%)	Human Blood Serum.	Human Blood Serum + 0.3% Iodine.	Gelatin 5% Dis- tinctly Acid.	Gelatin 5% Acid Weak Iodine.	Gelatin 5% Acid + Weak Fuchsin.
1 day	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis
2 days	"	"	"	"	Some autolysis	"	"	"	"
3 days	"	"	"	"	Complete auto- lysis	Some autolysis	"	"	"
7 days	"	"	"	"	"	Complete auto- lysis	Slight auto- lysis	"	"
14 days	"	"	"	"	"	Some auto- lysis	Some auto- lysis	Slight autolysis	Slight autolysis
33 days	Marked autoly- sis (infected)	"	"	"	"	Considerable autolysis	Complete au- tolysis	"	"
41 days	"	"	"	"	"	"	"	Some autolysis, but majority discrete	Some autolysis, but majority discrete
50 days	"	"	"	"	"	"	"	Considerable au- tolysis	Considerable au- tolysis

TABLE V
SUSPENSION OF GONOCOCCI KEPT IN THE ICE-CHEST

Time.	Gelatin 5 % (Acid).	Tragacanth Suspension.	0.6 % NaCl.	0.6 % NaCl+0.5 % Car- bolic Acid.	Ringer's Solution -0.3 % Triresol.
5 days	No autolysis	No autolysis	No autolysis	No autolysis	No autolysis
1 month
2 months
3 months	Slight autolysis with swollen forms	Slight autolysis
4 months	Some autolysis and swelling	Considerable auto- lysis and swelling
5 months				Considerable auto- lysis and swelling	
6 months					

After these experiments it seemed that the autolysis of the gonococcus was due to an enzyme which acted strongly in an alkaline medium, but which was inhibited in an acid medium. Shortly after this, however, having become acquainted with Warden's work which appeared to contradict the enzyme theory, further experiments were necessary. It was apparent that alkali caused autolysis and that acid inhibited it. This, however, was also explainable by Warden's hypothesis, since alkali would rapidly saponify and dissolve the fatty substance which he conceives to form the limiting membrane of the gonococcus. If such a fatty membrane exists, then one would expect it to be destroyed more rapidly with strong than with weak alkali, whereas if it is destroyed by an enzyme which acts in an alkaline medium, then one would expect the destruction to occur gradually rather than quickly, and also that the enzyme would act better in a moderately weak alkali than in a strong solution of the latter. To settle this question the following experiments were performed:—

(a) A luxuriant growth of gonococci from a slope culture was shaken up with beads in $\frac{N}{20}$ sodium hydroxide, with the result that the gonococci were dissolved quickly.

(b) A similar luxuriant growth was shaken up with beads in $\frac{N}{10}$ sodium hydroxide and the gonococci were dissolved almost instantaneously. It is inconceivable that this extremely rapid dissolution of the gonococci could be due to an enzyme, so it would appear that Warden's idea regarding the fatty envelope may be correct. The alkaline solution of the gonococci was somewhat soapy and yielded a copious and permanent froth on shaking. Moreover, when acid was added a copious precipitate was produced. The author believed at first that this precipitate consisted of fatty acids. This, however, was disproved, since the substance was insoluble in sodium carbonate and also insoluble in alcohol, ether, and acetone.¹

The deposit was amorphous, and on staining proved to be Gram-negative.

(c) A culture of a Gram-negative bacillus of the *B. coli* type was emulsified in $\frac{N}{20}$ sodium hydroxide and shaken up with glass beads. The bacilli were eventually dissolved by the alkali to form a clear solution, but this took several hours.

(d) A culture of a Gram-positive coccus of the pneumococcus type obtained from urine was shaken up with beads in $\frac{N}{20}$ sodium hydroxide and the organisms remained undissolved, leaving an opaque emulsion. This organism was still undissolved several days later.

(e) A culture of staphylococcus albus (Gram +) was treated similarly and remained

¹ Since this chapter on autolysis was written the author's researches have advanced very much further on the lines of the biochemistry of the germs; *vide Lancet*, 16th and 23rd April 1921. Warden's view that the gonococcus consists largely of fatty and lipid substances is untenable.

undissolved by the $\frac{N}{20}$ sodium hydroxide. A culture of a yeast (Gram +) gave the same result, remaining undissolved.

Hydrochloric acid ($\frac{N}{20}$) had no dissolving effect upon the gonococcus; on the contrary, it rather tended to produce flocculation, thereby increasing the amount of deposit on standing.

This acid did not dissolve the Gram-positive organisms, nor did it cause flocculation to the same extent.

Warden (1915) analysed the gonococcus chemically. He found that 0.501 gramme air-dried gonococcus yielded 0.0647 total nitrogen (Folin's method) and 0.0261 fatty acids.

McClintock and Clark stated that washings of the gonococcus in saline gave a copious precipitate when acidified with acid and heated, and they considered that this was a precipitate of protein substances.

If Warden's view that the limiting membrane consists largely of a species of fatty acid is correct, this would explain why the germ is soluble in alkali, whereas it remains unchanged in a weak acid like sodium phosphate. Disintegration also occurs in water and saline, but much more slowly, and this, according to the fatty acid hypothesis, possibly depends on the proportion of hydrogen and hydroxyl ions present in the solution; if the latter predominate, then saponification of the fatty membrane with consequent autolysis will occur more quickly. At any rate alkali is harmful to the gonococcus, while weak acid is favourable to it.

Practically all of the more recent workers on the cultivation of the gonococcus agree that the germ flourishes best on a medium brought to a reaction of about +6 acid (Eyre's scale). Finger (1905) appears to be responsible for the belief that a slightly alkaline medium is most suitable for the development of the gonococcus. He states that the slight acidity in the urethra, due to the acid urine, is rendered alkaline by the secretion of the urethral glands during coitus, and that this alkalinity, which is most suitable for the gonococcus, renders the mucous membrane more apt to be infected by the germ.

It seems, however, that this belief must be abandoned, since the scientific evidence deduced from direct experiment is entirely against it, and on the contrary it would appear that alkali is very destructive to the gonococcus. Even a solution of 1 in 3000 sodium bicarbonate will autolyse them fairly rapidly.

So far, then, we have three reasons laid down for the autolysis of the gonococcus. Flexner and Wollstein believe that it is due to an intracellular enzyme. Warden thinks it is due chiefly to hydrolysis from water, and the author's belief is that the most potent factor is the alkalinity or excess of hydroxyl ions in the surrounding medium. It is quite likely, however, that it may be due to all of these causes. Flexner has brought forth considerable support in favour of the enzyme view, which must not be overlooked. For example, when the gonococcus is grown on a solid +6 acid medium, the surface growth autolyzes in a few days, yet it is found that the medium is still acid. Here, therefore, the autolysis cannot be attributed to alkalinity, and we have to rely on the enzyme explanation, or upon the process of hydrolysis.

In reality the processes of disintegration from hydrolysis or due to alkalinity are much the same, since both, so far as one can gather from the works on colloid chemistry, depend on the ionic concentration. Alkali means excess of hydroxyl or cations, and acid means excess of hydrogen ions—anions, the former destroying the limiting membrane of the gonococcus, whereas the latter preserve it.

A gonococcal vaccine put up in 0.6 per cent acid sodium phosphate does not readily become an autolysate. Such a vaccine, even after it has stood at room temperature for three weeks, when centrifugalised leaves a clear supernatant fluid which gives only the

faintest trace of precipitate on the addition of stronger acid, and when tested according to the method of McClintock and Clark by heat and the addition of acetic acid gives only the very faintest trace of precipitate. These tests show that very little autolysis occurs in such a vaccine even after it has stood for a considerable time at room temperature.

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CHAPTER IX

SUGAR FERMENTATION REACTIONS AND THE ALKALI TEST

GONOCOCCUS, MENINGOCOCCUS, MICROCOCCUS CATARRHALIS, ETC.

Sugar Fermentation Reactions.—Rothe (1905) first showed that the gonococcus could be distinguished from the meningococcus in that the latter fermented maltose whereas the former caused no change. Kutscher (1907) was able to verify Rothe's declaration with 28 different strains of gonococci. For this test, fermentation tubes containing a good liquid medium are required, and the various sugars are added along with some indicator such as litmus. A satisfactory liquid medium would be one containing 1 per cent peptone water, 0.5 per cent disodium hydrogen phosphate, and brought to a reaction neutral to litmus. Also fresh human serum or plasma should be added in the proportion of about 1 in 5 to 1 in 10. One to two per cent of the various sugars are required, and also litmus about $\frac{1}{10}$ per cent. The tubes should be inoculated fairly heavily.

Wollstein (1907) found that the gonococcus did not grow on sheep's-serum water containing sugars; so she had to use a human-serum litmus water for the fermentation tests.

Watabiki (1909) used a horse-serum peptone water, but Martin (1910) thinks that this medium is unreliable for the sugar reactions. Cole and Lloyd used their tryptamine-blood-extract broth and employed phenol-sulphonephthalein as the indicator instead of litmus. Martin used solid media for the fermentation tests and preferred them to the liquid. He states that if drying is prevented by the use of india-rubber caps, there is little or no tendency for the solid cultures to turn acid and then become alkaline at places, as observed by other workers, such as Arkwright (1909), etc. He says that solid media possess the great advantage that the nature and extent of the growth can be observed from the beginning, and where serum is a constituent one can see better that there are no contaminations.¹ Further, with delicately growing strains it is necessary to be sure that growth has taken place, and fluid media are not the best for observing this in the case of the gonococcus. A point of the greatest importance in the preparation of these media, he states, is to avoid alteration of the composition of the fermentable sugars in the process of sterilisation. They should be sterilised separately in distilled water for ten minutes at 110° C. and then added to the sterile agar medium. It is better to use Jena glass vessels, and these should be well steamed before use, as ordinary glass yields a considerable amount of alkali to a fluid during sterilisation. The sugars must also be of the purest products. Beef extract contains fermentable carbohydrates, so it is better to use in the medium only pure peptone water. The litmus should be sterilised separately in the autoclave at 110° C. for ten minutes.

Martin states that with his solid litmus medium he obtained very uniform results, as shown on the following table:—

¹ The author agrees entirely with Martin's statements, and has obtained good results by putting the various sugars in solid agar plasma medium containing various indicators, such as phenol red and brom-thymol blue, which change in colour around the neutral point.

		Mono-saccharides.											Di-saccharides.			Poly-saccharides.				
		Glycerine.	Erythrite.	Alonite.	Arabinose.	Xylose.	Mannite.	Dulcine.	Sorbit.	Dextrose.	Levulose.	Galactose.	Amygdaline.	Salicine.	Saccharose.	Lactose.	Maltose.	Raffinose.	Dextrin.	Inulin.
Gonococcus 34 strains .		o	o	o	o	o	o	o	o	+	-	o	o	o	-	o	-	o	o	o
Gonococcus 1 strain. .		o	o	o	o	o	o	o	o	.	=	o	o	o	-	o	-	o	o	o
Meningococcus 31 strains		o	o	o	o	o	o	o	o	+	=	o	o	o	=	o	+	o	o	o
Micrococci Catarrhalis Strains.	7 strains true catarrhalis .	o	o	o	o	o	o	o	o	-	=	o	o	o	.	o	.	o	o	o
	10 strains atypical catarrhalis .	o	o	o	o	o	o	o	o	+	+	o	o	o	+	o	+	o	o	o
	2 strains atypical catarrhalis .	o	o	o	o	o	o	o	o	.	+	o	o	o	.	o	+	o	o	o
	2 strains atypical catarrhalis .	o	o	o	o	o	o	o	o	+	-	o	o	o	=	o	+	o	o	o
	2 strains atypical catarrhalis .	c	o	o	o	o	o	c	o	+	-	o	o	o	=	o	+	o	o	o

+ denotes acid but no gas, - indicates a slight alkaline reaction, and = indicates a marked alkaline reaction.

It will be noted that one of his 35 strains of gonococci which was isolated from a knee joint with supposed gonorrhoeal arthritis gave the typical *M. catarrhalis* fermentation. This organism also grew at 24° C. Hence it was certainly a very atypical strain of gonococcus. Mallory and Wright (1904) isolated a somewhat similar coccus from a knee with supposed gonorrhoeal arthritis, which grew easily on plain agar, and which they therefore considered not to be the gonococcus. Unfortunately they did not test its fermentation reactions. Broughton Alcock's aberrant strain, which grew easily on plain agar, only fermented glucose in ordinary meat broth.

Martin's fermentation results with regard to the gonococcus and meningococcus are in agreement with the results obtained by v. Lingelsheim (1906), Brons (1907), Rothe (1908), Elsler and Huntoon (1909), v. Stabsarzt and Kutscher (1909). Martin states that the least consistent results have been obtained by those who used fluid media. Arkwright (1909), Wollstein (1907), and Gurd (1908) each record a gonococcal strain which fermented both maltose and dextrose. Gurd had also five gonococcal strains which fermented dextrose and galactose; Gordon (1905) and Shennan and Ritchie (1908) also each record one strain which fermented galactose as well as dextrose. Mayou (1908) states that the gonococcus produces acid with glucose and galactose, the meningococcus gives acid with glucose only, and the *Micrococcus catarrhalis* gives no reaction with either. Watabiki (1909) studied 15 strains of gonococci which all fermented dextrose, maltose, dextrin, and levulose, while galactose, lactose, saccharose, mannite, dulcine, and inulin were unaffected, but Martin considers the medium he used was unreliable.

Cole and Lloyd (1917), using their own fluid medium, found that the gonococcus fermented glucose and galactose in twenty-four hours, and gave slight fermentation with maltose and sucrose after forty-eight hours.

With regard to the meningococcus the vast majority of workers agree that both dextrose and maltose are fermented. (Gordon (1905), v. Lingelsheim (1905), Andrewes (1906), Dunham (1906), Goodwin and von Sholly (1906), Kutscher (1907), Stoevesandt (1908), Symmers and Wilson (1909), and Arkwright (1909).)

Differences exist regarding galactose, levulose, and dextrin, but Martin states that in such cases due care was not taken with regard to ensuring the purity of the sugars.

Arkwright noted that certain strains of the meningococcus mutated on artificial cultivation, the fermentation reactions changing after some months of artificial growth.

With regard to the rate at which the fermentative changes occur, Martin states that

with the meningococcus and *M. catarrhalis* the results are usually well marked in forty-eight hours, while the gonococcus requires four to five days. He finds that no indol is produced by any of these three groups of organisms.

The Alkali Test.—The gonococcus is extremely soluble in alkali, so when there is any difficulty regarding the nature of a given strain it is useful to test its solubility in $\frac{N}{20}$ sodium hydroxide. A true gonococcus culture will dissolve rapidly when shaken up in a few c.c. of this fluid to form a clear solution. The meningococcus also dissolves easily, but the solution appears to show more of a milky turbidity. The organisms of the *M. catarrhalis* group, on the other hand, do not dissolve but leave an opaque white emulsion.

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CHAPTER X

THE VITALITY OF THE GONOCOCCUS

DRYING—MOISTURE—LOW TEMPERATURE—HIGH TEMPERATURE—INFLUENCE OF FEVER—
THERMO TREATMENT—INFLUENCE OF CERTAIN LIGHT RAYS

THE gonococcus is fortunately very sensitive to drying. In pus which has been allowed to dry up even for quite a short time, the germs according to Scholtz (1903) are always found to be dead. Haberdar (1894) found that in pus stains on dry linen, the gonococci had lost their vitality even after an hour, and death occurred as soon as the pus had dried up.

According to Finger, Ghon and Schlagenhauser (1894), the organisms will remain alive in purulent discharges only so long as the pus retains some moisture. In one authenticated but very rare occasion, however, a successful culture was obtained from dried pus after seventy-two hours.

Findley (1908) points out that there is considerable difference of opinion amongst certain experts with regard to their resistance to desiccation.

Kratter (1894) and McFarland believe that the germ can live for a long time even in dried secretion; Findley himself maintains that they die very rapidly when dried.

Steinschneider and Schäffer (1895) found that gonococci exposed to drying retained their vitality only up to five hours at the longest, and most authorities are in agreement on this point. The germ certainly does not long survive complete desiccation. Of course, where the pus does not dry up very quickly, as on the skin, on linen, and various utensils, the gonococci will certainly remain alive for several hours at least.

In moist conditions, on the other hand, the organism will live in pus for a considerable time. Cultures can certainly be obtained from moist gonorrhœal pus which has stood at room temperature for several hours, and in some cases after twenty-four hours.

Steinschneider and Schäffer maintain that the gonococci in pus can retain their vitality in warm bath water or in urine for one to two hours.

According to Stein quoted by Jadassohn (1910), the germs can be cultivated from non-albuminous urine after seven but not after nine hours. If the urine is albuminous they can be cultivated from it after twelve hours. In concentrated urine, however, he was unable to cultivate them after three hours. The author has pointed out in Chapter VIII. on autolysis that the vitality of the gonococcus in urine depends largely upon whether the latter is acid or alkaline.

Neisser and Scholtz (1903) showed that the germ died rapidly when dried, but lived for twenty-four hours when moist.

Bacteriological evidence therefore goes to show that the disease may be carried by baths, sponges, moist towels, rectal thermometers, bed linen, diapers, night-clothes, etc. Alice Hamilton (1908) has emphasised the importance of scrupulous cleanliness in these matters, more especially in institutions for young girls. Many epidemics of gonorrhœal vulvo-vaginitis have been traced to the use of common baths, towels, sponges, etc.

Dowd (1921) cites two cases of young women who undoubtedly in his opinion con-

tracted gonorrhœa from bathing in a tub in which some one having gonorrhœa had taken a bath previously. The infective purulent material had adhered to the tub, thus infecting these two young women.

Free gonococci die much more quickly than when incorporated with pus. They die in a few hours when shaken up in water or in normal salt solution.

Warden (1915) maintains that free gonococci from cultures live longer when incorporated or protected with anhydrous substances such as oils, ointments, etc., and he holds that for this reason ointments are not suitable for prophylactic purposes. This would be true enough if the ointments contained no antiseptics, but they undoubtedly are destroyed rapidly by mercurial ointments, etc.

Free gonococci die after a few days even under the most favourable cultural conditions in the incubator, as already pointed out in Chapter VI. They die out most rapidly where the growth is most profuse, but they live for long periods of time where growth is very slow, as *in vacuo* and in stab cultures.

A culture may remain alive for two or three days at room temperature, and for still longer periods in the ice-chest and at temperatures below freezing-point (see Chapter V.).

M. Wassermann (1901) succeeded in cultivating the gonococcus from the aortic valve of a heart which had been kept in the ice-chest for twenty-four hours.

The virulence of gonococci on artificial media is retained for a considerable time. Wertheim (1901) was able to produce a typical gonorrhœa in a man by inoculating the urethra with a culture which had been growing artificially for four weeks. Finger, Ghon and Schlagenhauser had the same success with a five-months-old strain which had been kept growing on serum agar. Most workers agree that the germ gradually loses its virulence when grown artificially, but the above experiments show that it can remain infective although cultivated artificially for a very long period.

Although the gonococcus can survive a long exposure to cold it is nevertheless extremely susceptible to even moderately high temperatures. According to the observations of Kiefer, Schäffer and Steinschneider, Finger and Scholtz, it is killed by a few hours' exposure to a temperature of 40-41° C., even when the temperature is raised quite gradually. The contrary statements of Wertheim that it can thrive in the culture tube at a temperature of 39° to 40° C. and over, and that it can withstand heat up to 42° C., have so far found no support.

The gonococcus appears to be able to withstand greater temperatures when living in the body than under cultural conditions. At any rate in the human body itself the gonococcus can sometimes survive a constant fever heat of 40° C. and over. It has been noticed, however, that high fever has a retarding influence on the disease. When there is a high temperature the urethral discharge often vanishes almost completely. Neisser and Scholtz found that it was more difficult to obtain cultures from patients during fever than when the temperature was normal. Finger, Ghon and Schlagenhauser regularly failed to produce experimental gonorrhœa by artificial inoculation of the urethra with cultures of gonococci when the patient had a temperature of 102.2° to 104° F. When no fever existed, however, the artificial infection always succeeded.

Bogdan (1893) quotes a case in which the gonorrhœal discharge disappeared during an attack of pneumonia with high fever, and returned when the fever had abated.

Guiard (1894) describes a case where the discharge cleared up during an attack of scarlet fever and remained cured.

On the other hand, Nicoll (1915) described three cases of gonorrhœal septicæmia with arthritis following scarlet fever.

Luis (1913) observed a case where, with an attack of mumps and a high temperature of 104° F., the discharge disappeared, but returned again after the fever had gone.

Nobl (1901) published a series of five cases of gonorrhœa complicated by various febrile affections (pneumonia and pulmonary tuberculosis). In these cases the gonorrhœa was in no way influenced with regard to its virulence, although in all cases there was a

prolonged high fever of 104° F. On the other hand, Noguès (1908) published an account of two cases of gonorrhœa in which high fever led to a spontaneous cure. In spite of some contradictory evidence it seems pretty certain that the gonococcus can survive a temperature of 104° F. (40° C.), at any rate within the human body. Higher temperatures than this would appear to be definitely harmful to the germ.

Culver (1917) states that the optimum temperature for gonococci is 97° to 98° F., and that a sudden increase of temperature to 102° F. or over causes certain death of the culture. He also mentions a case of gonorrhœa which recovered after having malaria for four days with a temperature of 105° F. He says that one rarely, if ever, sees a gonorrhœal infection coexisting with some other fever, such as pneumonia, typhoid, or malaria. Attempts have been made to apply this susceptibility to heat in therapeutics (see Chapter XXXV.).

Muller and Weiss (1916) produced a temperature as high as 104.7° F. in six to ten hours by the intra-gluteal injection of boiled milk or sodium nucleinate. Satisfactory results were obtained in epididymitis, prostatitis, and arthritis by repeated injections of these substances.

Boermer and Santos (1914), using a diathermic apparatus, found that the gonococci in the urethra were killed when subjected to a temperature of 102.2° F. for ten hours. Three hours at 105.8° F. and fifty-seven minutes at 107° F. caused the same results. Local gonorrhœa has been treated in this way with considerable success.

The gonococcus appears also to be easily killed by certain actinic rays, such as "X"-rays and the ultra-violet light—Russell and Nichols (1912).

Attempts at treatment in this direction have been carried out so far with indifferent success.

The susceptibility of the gonococcus to various chemicals will be dealt with in Chapter XXXV. on chemical treatment.

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CHAPTER XI

THE TOXINS OF THE GONOCOCCUS

ENDOTOXIN OR EXOTOXIN?—METHODS OF OBTAINING GONOTOXIN—RESISTANCE TO HEAT—ANIMAL EXPERIMENTS—URETHRAL INJECTIONS—AUTHOR'S EXPERIMENTS—FALLACIES WITH REGARD TO THE ISOLATION OF TOXINS FROM GERMS

THE gonococcus is a very toxic organism, and, quite apart from the activity and multiplication of the germ, there is no doubt that the toxins alone produce many symptoms.

As early as 1866 Pidoux called attention to the general toxic effects of gonorrhœa, which resulted in pallor of the face, wasting, etc.

Other general toxic symptoms are fever, headache, pains in the joints, and even vomiting. These effects can be observed even in a normal person after the injection of a large dose of gonococcal vaccine.

Further, many writers maintain that gonorrhœal hyperkeratosis, iritis, and sometimes ophthalmia are caused, not by the actual presence of the gonococcus itself at the locality affected, but by the circulating toxins of the organism. This matter will be discussed in a subsequent chapter.

When live gonococci are injected into animals, no definite disease is produced. Apparently no animal except man is a suitable host wherein the germ may live. The symptoms produced in animals by the injection of live gonococci are not due to the multiplication of the germ, but are brought about to a large extent by the toxins.

(1) **Endotoxins or Exotoxins?**—If the gonococcus is cultivated for two to three weeks in a suitable fluid medium such as ascitic broth, the filtrate will be found to be more or less toxic for small laboratory animals. With the exception of one investigator, it is generally agreed that this toxic substance is derived entirely from the dead or disintegrated bodies of the gonococci, and is not a physiological product of the living organism. In other words, they consider that the poison is an endotoxin which is only set free when the germs autolyse, and not an exotoxin which is secreted naturally during the life and growth of the coccus. Finger, Ghon, and Schlagenhauser (1894), Nicolaysen (1897), A. v. Wassermann (1897-98), Scholtz (1899), Wildbolz (1902), and Torrey (1908) support this view. De Christmas (1897) and (1900), however, by the use of a special culture medium, claims that the gonococcus may produce, by a biological process, an extracellular poison or exotoxin, which when injected into guinea-pigs, etc., is extremely fatal. He concluded that the poison was an exotoxin, because it could be detected in gonococcal filtrates of serum bouillon cultures within twenty-four hours.

Morax and Elmassian also hold that a certain amount of toxin escapes into the culture fluid. The endotoxin adherents, however, maintain that this is due to the fact that the gonococcus commences to autolyse very early, within the first twenty-four hours.

(2) **Methods of obtaining Gonotoxin.**—De Christmas at first used a fluid culture medium composed of ascitic fluid 1 part and peptone water 2 parts. Later, however, he concluded that peptone and salt had an inhibiting influence on toxin production, and he preferred a mixture of ascitic fluid and meat bouillon prepared as follows:—

Macerate 500 grammes of fresh minced veal (salt free) in 1 litre of warm water, add 2 to 3 grammes of gelatin. Heat to 105° C. for one half-hour. Filter, sterilise, and concentrate to one-quarter of its original volume. Mix 25 parts of this bouillon with 75 parts of ascitic fluid.

The gonococcus did not grow well in this medium unless it was first acclimatised to it by successive passages through bouillon containing first one-quarter and then one-half of its volume of ascitic fluid. After acclimatisation its resistance and toxic properties increased. It lived in the above medium for about forty days, and the maximum toxicity was obtained towards the twentieth or thirtieth day of incubation at 37° C. The toxic filtrate was obtained by passing the fluid culture through sterile talc.

Cantani (1899), Vannod (1907), and Torrey (1908) after various experiments concluded that no enhanced virulence was secured by using the special bouillon formula recommended by De Christmas. Wildbolz (1902) found that more toxicity was produced in Thalmann's broth 2 parts, plus ascitic fluid 1 part, than in Thalmann's broth alone without ascitic fluid. Torrey maintained that the filtrate of the medium in which there was the greatest growth and hence the most active disintegration of cocci contained the maximum amount of toxin; and, contrary to the opinion of De Christmas, he found that peptone increased the growth and hence the toxicity of the culture.

Morax and Elmassian obtained an active toxin by allowing gonococci to macerate for eight to ten days in an alkaline solution (potash 1 per cent). Nicolaysen by drying and grinding up the germs was able to obtain the endotoxin in concentrated dried form.

(3) **Resistance to Heat, and other Observations.**—Nicolaysen found that the toxin remained active after complete drying, and that it could withstand a temperature of 120° C. for a short time, and still remained toxic after a considerable exposure to 100° C. De Christmas stated that his toxic filtrates withstood a temperature of 65° C. for fifteen minutes, but that they were somewhat changed when heated to between 65° C. and 75° C. A temperature of from 75° C. to 80° C. rapidly destroyed the toxic properties. The toxin was able to dialyse through parchment. It possessed the property of diastase. Strong alcohol and sulphate of ammonia precipitated the poison in the filtered cultures.

Flexner (1907) found that an autolysate of meningococci, filtered and centrifuged to get rid of the sediment, was lethal to guinea-pigs. Heating this autolysate to 65° C. did not materially reduce the toxicity. He concluded that the toxin was probably not an enzyme. Since the toxic action of the cocci depended upon disintegration, he considered that reduction in the rapidity of dissolution might render them less poisonous. Live meningococci proved to be more lethal on injection than the autolysate. This was, in his opinion, due to the fact that the live germs multiplied for some time after the inoculation. At any rate he considered that this explanation was more reasonable than the assumption that the toxin deteriorated quickly after the death of the cocci.

Wollstein (1907) applied Flexner's researches to the gonococcus and obtained somewhat similar results.

Torrey (1908) found that living gonococci were more toxic than the dead germs when injected intraperitoneally into a guinea-pig. He states that the difference in toxicity is probably due to the living gonococci being more invasive and less readily disintegrated than the dead ones; the toxin accordingly would be carried to vital points before being freed from the cocci by lytic agents.

(4) **Animal Experiments.**—Gonotoxin is very toxic to laboratory animals which are resistant to infection with the gonococcus itself.

Nicolaysen estimated that the minimum lethal dose of his desiccated toxin was 0.01 gramme for mice. De Christmas found that guinea-pigs, mice, rabbits, and goats were all susceptible to the poison. A subcutaneous or intraperitoneal injection of 1 to 2 c.c. of his culture filtrate sometimes killed a guinea-pig. As a rule, however, the lethal dose was 5 to 10 c.c. of the filtrate of a very rich serum bouillon culture. Usually there was an initial rise of temperature before death, but with very large doses the temperature

tended to remain sub-normal. Death occurred, as a rule, within twenty to thirty-six hours. With mice $\frac{1}{2}$ to 1 c.c. of a rich bouillon culture was usually fatal. Death was also caused in rabbits in the same way by intravenous or intraperitoneal injections, but as a rule the action was not so prompt. When injected subcutaneously into guinea-pigs and rabbits there was produced at times a more or less definite infiltration at the spot, which occasionally led to necrosis and abscess formation. When injected into the brain $\frac{1}{500}$ of a c.c. killed a guinea-pig in four to six hours. According to Nicolaysen, Schäffer, v. Wassermann, and Scholtz, injections of non-fatal doses produced in rabbits a rise of temperature, and eventually the animal lost weight. De Christmas obtained the same results with goats. No other characteristic effects were usually noted.

Moltschanoff (1899) reported that guinea-pigs and mice showed decided nervous symptoms after an injection of gonococci, but his observation has not been supported by others.

Injections of gonococcal toxin call forth characteristic manifestations in man. When injected subcutaneously, Wertheim noticed at the site of inoculation an erysipelas-like reddening and swelling.

v. Wassermann confirmed these observations, and described also a moderate rise of temperature, a more or less pronounced aching in the limbs and muscles, and painful inflammation of the glands. Bumm and Steinschneider, on the contrary, have seen such injections pass off entirely without symptoms, and Grosz and Kraus (1898) failed also to obtain any effect with injections of filtrates. The author has injected gonotoxin subcutaneously in men, and this was invariably followed by redness and swelling at the site of inoculation, within twelve to twenty-four hours.

(5) **Injections of Gonotoxin into the Urethra.**—De Christmas found that 2 c.c. of a dilution of gonotoxin (1 in 10), when injected into the anterior urethra and held there for two to three minutes, always produced a definite but transient urethritis. Repeated injections did not produce any signs of immunisation. Schäffer (1897) by injections of gonotoxin produced a marked exacerbation of a post-gonorrhoeal catarrh; and Panichi (1904) claimed that such injections produced a marked inflammation in the normal as well as in the chronic gonorrhoeal urethra.

Grosz and Kraus (1898) and also Scholtz ascertained that a purulent discharge occurred six to twelve hours after an injection of dead gonococci into the urethra. This discharge, however, passed off in twenty-four to forty-eight hours. These observers doubted the specificity of the results obtained by De Christmas, as similar results were obtained with injections of dead cultures of other germs such as staphylococci, *B. coli*, etc.

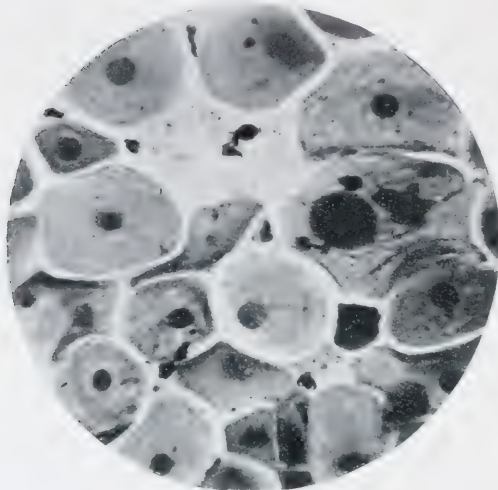
(6) **The Author's Experiments.**—(a) Eight slope cultures of the gonococcus, a week old, were emulsified in distilled water and kept for ten days. This more or less autolysed emulsion was passed through a Berkefeld filter and the filtrate made up to 20 c.c. This filtrate contained presumably endotoxin.

(b) Eight slope cultures of gonococci, twenty-four hours old, were emulsified in distilled water and filtered immediately through a Berkefeld filter. The filtrate was made up to 20 c.c., and contained presumably only exotoxin.

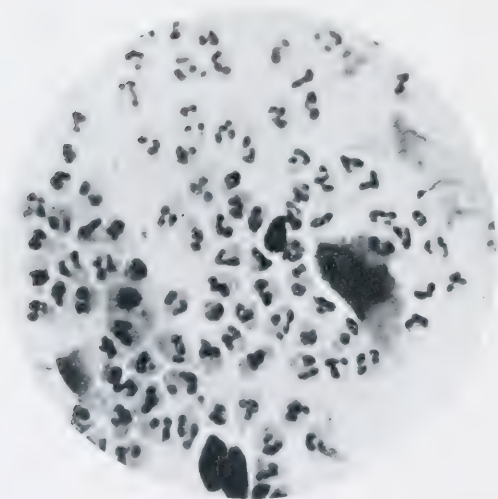
Experiment I.—A case of chronic gonorrhoea was selected in whom for some weeks there had only been a whitish morning drop consisting of epithelial cells. (No gonococci were detected.) Five c.c. of filtrate (a) were injected into the urethra and held there for twenty minutes. No pain was caused thereby, but four hours later a definite yellow discharge was obtained consisting almost entirely of pus cells, but no gonococci were detected. Twenty-four hours later the discharge had subsided, and consisted of mucus and a little pus. The urine, however, contained an unusually large number of shreds (see microphotographs Nos. 1 and 2, Pl. III.).

Experiment II.—The following week, when the discharge of the patient subjected to Experiment I. had subsided completely, 5 c.c. of filtrate (b) were injected into the urethra and held for twenty minutes as before. Four hours later a definite yellow discharge of pus cells again appeared, but no gonococci were found.

PLATE III



No. 1.—Smear of urethral discharge of an old chronic gleet. Stained Jensen's method. The smear shows epithelial cells only and no gonococci. Magnification = 500 diameters.



No. 2.—Smear from the same case as the above, taken four hours after the injection of gonococcus toxin. Note that the discharge is now definitely purulent. Magnification = 500 diameters.

These experiments, which were repeated on several different patients with always the same results, seem to confirm the observations of De Christmas, and appear to point to the possibility of the existence of an exo- as well as an endotoxin.

Experiment III.—A guinea-pig weighing 340 grammes was injected intraperitoneally with 1 c.c. of filtrate (a) without any definite injurious effect. Ten days later $1\frac{3}{4}$ c.c. were injected and the animal seemed little the worse.

The lethal dose was not determined.

(7) **Certain Fallacies with regard to the Isolation of Toxins from Germs.**—When germs are macerated or autolysed in water or saline, the filtrates therefrom are generally toxic, but it must not be assumed that this filtrate is a solution of the pure toxin only. Proteoses, albumins, and globulins are soluble in water, and may therefore be present and mixed with the toxin or poison. The author (1921) has shown that the proteoses are provocative and have also immunising properties, but these properties may not be characteristic of the pure poison as well. Vaughan has shown that the endotoxin is soluble in absolute alcohol. Proteoses, albumins, and globulins, however, are not soluble in absolute alcohol, and so must be quite distinct from the endotoxin in nature. It should be remembered, therefore, that the toxic filtrates (watery) from germs contain germ proteins mixed with the toxin, and to draw conclusions from experiments with such a mixture and attribute the results to the toxin alone is liable to be fallacious.

For further information regarding the endotoxins of germs and the endotoxin of the gonococcus, see Vaughan (1913), *Protein Split Products*, and Thomson (1921), *Biochemistry of Germs and Other Proteins*.

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CHAPTER XII

DIAGNOSIS OF GONORRHOEA

MICROSCOPIC DIAGNOSIS—CHEMICAL PROVOCATION—PROVOCATIVE VACCINE—CUTI-
REACTION—COMPLEMENT-FIXATION—OPSONIC INDEX—PRECIPITIN TEST—CULTURAL
DIAGNOSIS

Microscopic Diagnosis. In early cases of gonorrhœa of the urethral mucous membrane the diagnosis is generally simple. In the discharge of such acute recent cases there are usually no other organisms present besides gonococci, or at the most there are only a very small number of other bacteria. The characteristic grouping of the diplococci within the pus cells, the typical coffee-bean shape, the rapid and certain decolorisation with Gram's method, are sufficient alone to establish the diagnosis of gonorrhœa. When these typical microscopic characteristics are present, a further confirmation by culture is superfluous. According to Kratter (1890), Neisser and Scholtz (1903), Haberdar (1905), Finger and Kutscher (1909), microscopic examination in such typical cases is sufficient for medico-legal purposes.

v. Zeissl (1903), however, stands alone in holding that for legal purposes confirmation of the diagnosis, even in typical cases, is required by cultural methods.

Where one is dealing with acute inflammatory discharges from the genital mucous membrane, there can be no doubt that the microscopic examination of smears stained by Gram's method is sufficient for the diagnosis of gonorrhœa when typical gonococci are found in considerable numbers. On the other hand, if even on repeated examination the characteristic cocci are not demonstrated, that is not sufficient proof that gonorrhœa does not exist. In other words, one can by microscopic examination give a definite positive diagnosis, but it is dangerous to give a negative diagnosis, more especially in chronic cases, and in smears from the genital tract of females, where gonococci are very often difficult to detect.

In chronic gonorrhœa, where the discharge contains generally a considerable amount of mucus, it is good practice to examine the smears first with the low power in order to locate the small aggregations of pus cells, as the gonococci are found most readily in the latter.

According to Neuberger (1906) this is especially true with regard to the shreddy secretions from the alveolar glands.

In chronic gonorrhœa, microscopic diagnosis may be extremely difficult and even impossible. The gonococci have become so scarce that they are very difficult to detect, and moreover in this stage secondary organisms are usually abundant. In such chronic gleet cases it is exceedingly difficult to determine if the gonococcus has finally disappeared, and whether or not the condition is now entirely due to the secondary organisms. In these cases all efforts to find gonococci by microscopic and cultural examination of even urine deposits, shreds, and expressed prostatic secretion may entirely fail. Yet in these a true relapse may often occur in which gonococci again become apparent.

In females the diagnosis of gonorrhœa by smear examination is very difficult, yet with regard to this there is some difference of opinion.

Goll, quoted by Parke (1905), only found gonococci in 178 out of 1080 cases by smear examination, *i.e.* about 1 in 6 were positive. The results obtained by Gurd (1908) with smear preparations were very similar.

Kelley, also White and Martin (1906), claim that the diagnosis can readily be made by examination of the fresh-stained pus. On the other hand, Bumm (1897), Parke (1905), and Bandler (1908) state that it is only by means of the most elaborate and difficult bacteriological technique that the gonococcus can be isolated and differentiated in cultures from other organisms resembling it in morphology. Gurd (1908) agrees with the latter observers that gonorrhœa in the female can only be diagnosed with certainty by highly-skilled bacteriological technique. The author decidedly agrees with Gurd's conclusions, and, contrary to the opinions of Kelley and White and Martin, maintains that it is extremely difficult to diagnose gonorrhœa in the female by smear examinations, whether the sample of pus be taken from the urethra, vagina, or cervix.

The majority of such smears when examined by the microscope show myriads of organisms, diplococci and diplobacilli (Gram-positive and Gram-negative), and only a bold and inexperienced observer would dare to diagnose the presence of isolated gonococci in such a mass of bacteria. The diagnosis is only certain where numbers of gonococci are found intracellularly. These may be found in the early acute stage, but it is rare to find such a picture in chronic female cases. In the majority of chronic female discharges the author has found the smears negative to gonorrhœa or doubtful. Cultures made on slope tubes similarly gave negative results. The complement-fixation test, on the other hand, gave in the majority of cases positive results.

Norris and Mickelberg (1921) point out the great difficulty in finding gonococci in stained smears of chronic female cases even when examined by an expert. Without desiring to depreciate the value of staining methods in diagnosis, they believe that their usefulness has been considerably overestimated. From a practical standpoint they consider that all cases should be regarded as of gonococcal origin until proved otherwise.

Provocation by Chemical Irritants.—In suspected chronic cases where no gonococci can be detected, it is necessary to employ the so-called "provocative" methods. The method consists in one injection of a chemical irritant, usually silver nitrate.

The irritation of the mucous membrane causes congestion and a mechanical flow of fluid to the surface. In this way any gonococci which may be lying deeply situated in the glands of the urethra are liable to be dislodged. Further, the hyperæmia and serous infiltration of the mucous membrane are conducive to the multiplication of the germs, so that encysted or latent gonococcal foci are stirred up to renewed proliferation.

According to Neisser, Jadassohn, Scholtz, etc., the method at all events is extremely successful in certain cases (when combined with microscopic examination) in establishing whether or not a chronic urethritis is gonorrhœal, and therefore infectious.

Neisser, Touton (1896), Löwenhardt (1898), Scholtz, etc., are satisfied that the test is of value with regard to the question of marriage. Chemical provocation has been extensively used in order to detect gonococci in females, and it appears to be of considerable value.

Generally speaking, the microscopic smear diagnosis of gonorrhœa in women, especially in chronic cases, is very difficult and unsatisfactory. The examination of vaginal smears is almost without value, as they are generally negative in adults. It is much more important to examine the pus expressed from the urethra, or pus from the cervix and the cervical canal.

Provocative Vaccine Diagnosis.—A further method of diagnosis in latent chronic cases consists in the administration of a "provocative" dose of vaccine. This acts through the blood stream in a similar fashion to local chemical irritation by waking up any latent gonococcal foci, and the result, if gonococci are present, is an increased urethral

discharge on the following day. If, however, no gonococci are present the chronic discharge will remain unaffected. There is some difference of opinion amongst the various investigators as to the dose of vaccine required for this test. Irons (1906) gave a dose of 500 millions. Apart from local reaction in the urethra, he considered that a marked general reaction indicated gonorrhoea. In eight adults with no history of gonorrhoea he found that an injection of 500 millions produced no reaction. Stockman (1911) found that a dose of 20 to 50 millions caused very little general reaction in non-gonorrhoeal subjects, whilst 150 millions usually produced a distinct rise in temperature but no malaise or other symptoms. If a definite focal and general reaction was produced he considered this diagnostic of gonorrhoea. He points out, however, that the test dose is difficult to define, since the reaction produced varies with the patient and also with the vaccine used. These difficulties seriously impair the value of the method.

Aronstam (1908) considers that a dose of vaccine is a powerful aid to diagnosis in latent cases of urethritis and in joint cases. Increased discharge and increased pains in the joints indicated a gonococcal condition. He considers the method a valuable one in testing cases for matrimony. He states that the dose must vary according to the individual. Mainini (1909) states that vaccine arrests the joint pains in cases of gonococcal arthritis, and that this specific action might be useful for differential diagnosis in doubtful cases of joint affections.

Menzer (1911) states that every gonorrhoeal patient after his course of treatment should be tested with a provocative dose of vaccine to test if he is cured.

Köhler (1911), Eising (1912), Ziemann (1912), Guggisberg (1912), and Müller (1912) all consider that vaccine is valuable for diagnostic purposes.

Reiter (1911) and Van de Velde (1912) consider that the value of vaccine in diagnosis is limited.

Frome (1912) concludes, from observations on 60 cases of gonococcal affections of the female adnexa, that local subcutaneous reaction is of no value, and that focal reaction is doubtful. He considers, however, that a rise of temperature beyond 38° C. after a dose of 0.5 c.c. of Reiter's vaccine or of 3 c.c. of arthigon is diagnostic of a recent tubal infection.

Slingenberg (1912) maintains that a diagnostic course of inoculation with progressive doses which fail to induce any reaction can be accepted as excluding gonorrhoea.

Fronstein (1913) says that gonococcal vaccine injected subcutaneously gives a general and focal reaction in gonorrhoeal subjects. The proper dosage is of great importance, but must be varied according to the stage of the disease, whether acute or chronic, and also according to the type of vaccine employed. He used several commercial vaccines, and found that a dose which produced a definite local and temperature reaction in gonorrhoeal subjects caused no reaction whatever in healthy persons. He considers the reaction as positive when about seven hours after injection there is a rise of temperature of 1.3° F. and over, as well as local and focal manifestations. Thus in 14 out of 30 cases there was an increased urethral discharge in which gonococci were found, whereas previous to the injection the germs could not be detected. In 5 cases he obtained a rise of temperature and increased pain in the testicles. In 2 cases pain occurred in the joints which had been involved three years previously. In 4 cases no reaction was produced and the diagnosis of gonorrhoea was rejected. He concludes that provocative gonococcal vaccine ought to be considered as a standard diagnostic method in gonorrhoeal lesions.

Neu (1913), after an extensive trial of gonococcal vaccines in the gynæcological clinic at Heidelberg, is rather sceptical, and concludes that no vaccine has yet been produced that is certain in diagnosis, or effective in the treatment of chronic gonorrhoea in the female.

Frühwald (1913) and Shattuck and Whittemore (1913) believe in the value of vaccine diagnosis.

Hauser (1913) considers that the provocative vaccine test is very important for the

differential diagnosis of gynaecological affections. The reaction was always positive in recent gonorrhœa cases, and always negative when gonorrhœa could be positively excluded. In doubtful cases a general and focal reaction was in favour of a positive diagnosis. A positive focal reaction is the chief criterion. Out of a series of 95 patients the test failed in 4 and the results were doubtful in 5 cases, so that only in 9.5 per cent of the total was the reaction misleading or unsatisfactory. He warns, however, that a negative reaction does not always exclude gonorrhœa, as in some cases the lesions may be too old to react, or else the dose given is too small.

Klause (1913) found that provocative vaccine did not always give certain results. Definite cases of gonorrhœa sometimes gave no reaction, whereas a general, focal, and local reaction sometimes occurred in non-gonorrhœal subjects.

Kyrle and Mucha (1913), also Asche (1911), Frank, and Freund (1913), were impressed favourably with the diagnostic value of "arthigon" (a commercial gonococcal vaccine).

Semenow (1913) states that the first injection of polyvalent gonococcal vaccine gives a constant focal reaction in cases of gonorrhœal arthritis, and that it is therefore valuable for the differential diagnosis between chronic gonorrhœal arthritis and similar joint diseases.

Sommer (1913) maintains that the practical diagnostic value of intramuscular injections of gonococcal vaccine is limited. Intravenous injections of "arthigon" are of higher diagnostic value. In doses of 0.1 c.c. it causes in gonorrhœal adults a temperature rise of at least 1.5°C .

Brück and Sommers (1913) do not consider that a rise of temperature following the injection is definitely diagnostic of gonorrhœa, since in about one-half of non-gonorrhœal subjects the temperature rose to over 38°C . They also tested the vaccine intravenously. In 5 healthy non-gonorrhœal women who received an intravenous injection of 0.5 c.c. of "arthigon" the temperature in 3 cases rose to 38°C ., and in 1 case to 39.3°C . In 2 of these cases a rigor was produced. One might therefore conclude that the dose given was too great, yet with such a dosage no reaction was produced in 5 out of 32 gonorrhœa cases, although 4 of these were suffering from complications. They conclude, however, from observations on 60 cases, that as a rule gonorrhœa cases with complications give the greatest reaction. In non-gonorrhœal subjects the temperature does not generally rise more than 1.5°C ., and a rise of 1.5°C . and over speaks for the existence of gonorrhœa. In some cases of gonorrhœa they observed a double rise of temperature. They consider that the second rise is due to destruction of gonococci and the subsequent release of the toxins from the gonorrhœal focus, causing as it were a second mild vaccination effect.

Brahns (1913) states that the local subcutaneous reaction is of no value, as it occurs also in non-gonorrhœal subjects. The same may be said with regard to focal reactions. After an intravenous injection of vaccine the majority of gonorrhœal cases show a temperature rise of over 1.5°C ., but out of 15 non-gonorrhœal subjects 11 had also a rise of 1.5°C . and over. Two cases showed a double rise; one of these had never had gonorrhœa, the other had had the disease fourteen years previously, but had no symptoms for years. He considers that the temperature rise is of no diagnostic value.

With regard to the recrudescence of the urethral discharge after a provocative dose of vaccine, he tested this method in 82 cases. In 3 cases an intramuscular injection of "arthigon" 2 c.c., and in one case an intravenous injection, undoubtedly provoked a return of the discharge. These cases had been free from gonococci for fourteen, sixteen and twenty-four days respectively. In many other cases the injection provoked a return of the secretion, but he could not be sure that some of these cases were not coincidences.

Brandweiner and Hoch (1913) found that different strains of gonococci varied greatly with regard to the reaction produced.

Habermann (1914) got similar results with regard to rise of temperature as those obtained by Brück and Sommers. Out of 18 cases with no history of gonorrhœa, 9 had rises above 38°C . He also noticed occasionally a double rise. He considers that the

focal reaction is not of great value on account of its inconstancy. No better diagnostic results were obtained by intravenous injection than by the subcutaneous or intramuscular method. He states that a double rise of temperature had no diagnostic significance, since it may occur also in normal cases, but he thinks that an evening rise of temperature persisting till morning is of value.

Leslenyi and Winternitz (1914) employed for diagnostic purposes an intravenous injection of "arthigon" (0.05 c.c. in 1 c.c. of saline). Out of 25 cases of gonorrhoea the temperature only rose to 38° C. and over, in 10. The remaining 15 showed practically no temperature reaction, although many of them had gonococci present in their discharges. They found that the focal reaction was also indefinite. In a second group of 32 cases they gave a larger dose—0.1 c.c. The temperature rose more than 1.5° C. in 11, 1° C. in 9, and less than 1° C. in the remaining 12. In most of the normal control cases the temperature did not rise so high, yet in two controls it rose to over 38.8° C. They conclude that an intravenous dose of 0.05 c.c. is useless for diagnosis; doses of 0.1 c.c. are of some value when a good focal reaction is also obtained. As this occurred, however, in only about one-third of the cases, they consider that both reactions are of very limited value.

Stümpke (1915) considers that vaccine diagnosis is of some value.

Asch and Adler (1916) state that when gonococci cannot be demonstrated in the urethral discharge a "provocative dose" of vaccine will often promote the appearance of the organism in the discharge or in the urine. The dosage they usually gave was 50 to 200 millions, and the gonococci appeared from one to nine days afterwards. As a rule 50 to 100 millions elicited a response in two to four days.

Pastors (1918) diagnoses when gonorrhoea in the female is cured by injecting doses of 50, 100, and 200 millions of gonococcal vaccine respectively on three successive days. On the fourth day the secretions from the uterus obtained with a blunt curette are inoculated on to culture media, and smears for microscopic examination are also made. If these are all negative he is inclined to consider the patient cured.

Pearson (1918) got reliable results with provocative vaccine diagnosis in 96 per cent of cases. The doses of vaccine which he recommends are 3 millions on the first day and 5 millions on the second.

Müller (1920) states that a provocative reaction may be obtained in gonorrhoea with non-specific bacterial antigens, but there is danger of serious complications. An intracutaneous injection of bacteria and toxin-free milk protein is found to be a very effective agent in arousing a reaction in latent urethral gonorrhoea. There occurs only a moderate leucocytosis, but after six hours the patient experiences a slight itching in the urethra, following which there is a distinct increase in the discharge. Examination of this discharge will disclose the presence of the gonococcus if the infection is due to this agent. This procedure has yielded superior results over the customary methods now in use.

From the above mass of evidence one may conclude as follows:—

- (1) A local subcutaneous reaction is of no value in diagnosis.
- (2) A temperature reaction is of limited value.
- (3) A focal reaction, as a general rule, is significant and of considerable value.
- (4) An increase or recrudescence of a urethral discharge after a provocative dose of vaccine is practically a certain evidence that the disease is not yet cured, since a hypodermic injection of gonococcal vaccine will certainly not provoke a urethral discharge in a normal person.

The Cuti-reaction. This method is analogous to the cuti-reaction for tuberculosis introduced by von Pirquet. A glycerine extract of gonococci is introduced into the skin by means of a fine hypodermic syringe.

This reaction in gonorrhoea was observed by Brück (1909) in cases of epididymitis after injections of gonococcal vaccines.

Reiter (1911) also noticed it in gonorrhoeal pelvic infections in women.

Irons (1912) first experimented with glycerine extracts of the autolysed germs, and found that these gave much better results than when ordinary vaccine was used.

In positive cases an area of hyperæmia 5 to 10 mm. in diameter was obtained twelve to twenty-four hours after the injection. Frequently a definite papule developed. Control injections of glycerine alone showed only the needle puncture. In normal persons no reaction was obtained, or at the most only a slight area of redness of 2 to 3 mm. in diameter. He found that different strains of gonococci varied in intensity of reaction, and considers that a combined extract of many strains would be best for the test. In a further paper he states that in very early cases of gonorrhœa the cuti-reaction is negative, but develops gradually during the course of the disease. In the more chronic forms of gonococcal infections, such as arthritis, the degree of the reaction varies from day to day, and these variations may be correlated with the changes in the clinical course of the disease. Cases of severe infection, such as extensive arthritis, may give negative reactions, but later, when clinical improvement has occurred, the reaction becomes positive. A positive reaction is obtained in general at some time during the course of a gonococcal infection. Occasionally in adults, and somewhat more frequently in children, a fairly marked reaction is obtained where gonorrhœa can be definitely excluded. He considers that in such cases the normal antibodies may be increased to an unusual degree, and considers it likely that infections due to *M. catarrhalis* and the meningococcus might complicate the test. A meningococcal extract also gives the reaction, and suggests that it may be common to all this group of organisms. Finally, he considers that though further research is needed on this subject, yet a positive reaction is confirmatory evidence of a gonococcal infection.

London (1912) states that negative results are obtained by injection of gonococcal vaccine in saline, under the skin. When, however, the same vaccine is injected intradermally, very beautiful effects are produced in gonorrhœal subjects similar to the "stick" reaction obtained by Hamburger and by Naulheimer in tuberculin diagnosis. He injects a few drops of gonococcal vaccine (50 to 100 mils. per c.c. in saline) into the skin. In positive cases after twelve to forty-eight hours there develops an area of erythema from one to three inches in diameter, in the centre of which there is a small red papule somewhat deeper in colour than the surrounding areola. Often the entire area of reaction is slightly elevated, but the adjacent lymph nodes are not enlarged. In negative cases there is no reaction, or only a yellowish discoloration at the site of injection. Normal saline may be used as a control, but he considers this unnecessary, as he obtained no reaction in negative cases even with emulsions containing 500 million gonococci per c.c.

Sommer (1913) admits that the cuti-reaction obtained with gonococcal vaccine shows a certain amount of specificity, but maintains that the experimental results are so uncertain that the reaction is not of any very definite practical value. The ophthalmoreaction with gonococcal vaccine has no diagnostic value.

Finkelstein and Gerschun (1913) tried the cuti-reaction in 46 cases of gonorrhœa (22 acute and 24 chronic) and controlled the results in 38 non-gonorrhœal subjects. The technique consisted in scarifying the skin with a lancet in four places 2 to 3 centimetres apart, without drawing blood. To the four places were applied (1) control salt solution; (2) control streptococcus vaccine; (3) gonococcus vaccine 1 million per c.c.; (4) gonococcus vaccine 10 millions per c.c. The solutions were left on for ten minutes and then dried with cotton-wool.

In 35 out of the 38 non-gonococcal patients the reaction was completely negative, and 3 were weakly positive (reddening without any papule). Two of the latter admitted subsequently that they had urethritis, and another had shreds in his urine. Out of the 22 cases of acute gonorrhœa, 7, or 33.1 per cent, gave a positive reaction with the (10 mils. per c.c.) vaccine, and a higher percentage of positiveness was obtained in the chronic cases. In two cases a definite result was obtained with the (1 million per c.c.) vaccine. The controls with the streptococcus vaccine and with the saline were all negative.

They tried the test also with an antiformin gonococcal antigen, but the results were

not so good as with the ordinary vaccine. They consider that the use of fresh vaccine in this test is essential for success.

Finally, they maintain that the test is a specific one and is not obtained in other diseases.

Sharp (1914) got 10 positive results with the cuti-reaction out of 27 cases of vulvovaginitis in little girls. In these cases he found 22 positive by the cultural tests, 9 were positive to the complement-fixation test, and only 5 were positive in microscopic examination of smears. The second best result, therefore, in his hands was obtained by the cuti-reaction.

Cherry and Palma (1921) state that in the gynaecological clinic at the Harlem Hospital, New York, about 40 per cent of the operative work is done for chronic adnexal disease. From the history of these patients, and from signs of infection of the cervix, Bartholin ducts, and urethra, they assumed that the gonococcus is the etiologic factor in the production of this condition in the majority of instances. As an aid to diagnosis, they tried the cutaneous reaction and the complement-fixation test. They concluded that the former test was useless for diagnosis, and the complement-fixation test was not very satisfactory in their hands.

The Complement-fixation Test is certainly of very great value in diagnosis. See Chapters XXVIII., XXIX., and XXX.

The Opsonic Index Test.—This is not of much value in the diagnosis of gonorrhœa. The technique is troublesome and the results are somewhat indefinite. It is, however, of interest from the scientific point of view, and is of considerable value as a guide to treatment.

Irons (1908) found that the opsonic index in cases of gonorrhœal arthritis before administration of vaccine varied from 1 to 1.6; the average was 1.0. Injections of vaccine were followed by a sharp rise up to 2.5 or 3.0. He always got a rise in the index in affected cases after massage of the prostate, and a similar rise occurred after massage of a gonorrhœal joint. In a case of epididymitis with an opsonic index of 1.0 to 1.3, a sudden spontaneous rise occurred up to 2.9. This fell again two days later to 1.4 without any evident clinical changes.

Ruth Vail (1907) found that the opsonic index to the gonococcus in thirty normal individuals (300 examinations) ranged from 0.8 to 1.2. In cases of gonorrhœa the opsonic index reached its highest point after numerous injections of vaccine.

Hamilton and Cook (1908) state that the opsonic index is low in gonorrhœa, especially in the early acute stage and also in very chronic cases.

In 10 normal persons the average index was 0.93.

In 10 acute cases of gonorrhœa the average index was 0.44.

In 10 chronic cases of gonorrhœa the average index was 0.62.

The opsonic index usually rises in cases which are recovering from the disease, and a rise is sometimes caused as a result of vaccine treatment.

After an injection of vaccine there is a transient fall to about 0.37, with a decided rise later. After three injections varying from 5 to 25 millions the index may rise as high as 1.9.

Eyre and Stewart (1909) state that the opsonic index in gonorrhœa is very variable. It may rise very high and rapidly fall very low, especially due to exercise, which causes an auto-inoculation of enormously toxic doses of gonococci set free at irregular intervals and in varying quantities.

This exercise may cause a marked negative phase, which increases the susceptibility of the patients to the disease.

After an injection of gonococcal vaccine the index shows an immediate negative phase, lasting for thirty-six to forty-eight hours, followed by a rapid rise to 3 or 4 or even higher. Large doses produced a very pronounced fall to as low as 0.2 or 0.3, and the

negative effect is prolonged. They consider, therefore, that large doses of vaccine are dangerous.

Van de Velde (1912) considers that valuable information may be obtained in gynaecological cases with a small test-dose of vaccine whilst controlling the findings with the opsonic index. He states that an unusually low opsonic index generally indicates gonorrhœa, and that a diagnostic vaccine injection will decide the matter in dubious cases.

The Precipitin Test.—Robinson and Meader (1920) found a positive precipitin test in all cases where the gonococcus was found in the discharge; also in many where the history pointed to gonorrhœa, although the germs could not be detected microscopically.

Culture Diagnosis.—The microscopic diagnosis may be very difficult in certain cases of chronic gonorrhœa when, as often happens, only isolated Gram-negative diplococci are found in the smears. In such cases the microscopic picture is not sufficient for diagnosis even when the isolated cocci detected resemble the gonococcus. The researches of various authors have shown that Gram-negative cocci, like the gonococcus, may occur at times in the male and female genital tracts (these will be discussed in the next chapter). In these cases it is necessary to resort to cultural methods to confirm the diagnosis. Again, several authors assert that diagnosis by culture is more efficient in chronic cases than the repeated microscopic examination of smears. Jeckstadt (1904), Scholtz (1901), and Kutscher (1909) consider that to a certain extent the culture method is superior. The latter observer got cultures of gonococci on ascitic agar in 28 out of 67 cases of chronic gonorrhœa, *i.e.* 41·8 per cent positive. By microscopic examination, on the other hand, he found gonococci in 25 cases, *i.e.* 37·5 per cent were positive. Thus the cultural diagnosis was somewhat superior to the microscopic examination, but in 2 cases the cultures proved negative where gonococci were diagnosed with certainty in the smears with the microscope. Taking both methods together, gonococci were definitely demonstrated in 30 (44·8 per cent) out of 67 cases of chronic gonorrhœa.

Meyer (1903) obtained a higher percentage of positive results by culture. In 58 out of 90 cases the microscopic and cultural tests agreed exactly, and in the remaining 32 cases the cultures gave a further number of 28 positives where the microscopic findings were negative. In 3 cases gonococci were found in the smear preparations where the cultures failed.

Kutscher attributes the higher number of positive results obtained by Meyer to the fact that he was able to examine his cases more frequently.

Heinman (1895) in 61 cases of chronic urethritis found the gonococcus only fourteen times by cultivation.

Steinschneider (1898), after examining a series of cases of vaginal gonorrhœa in children, concluded that the culture method was superior.

Baermann (1903) obtained results which agree approximately with those of Kutscher. Ströhmberg (1901) claims to have demonstrated the presence of gonococci in 100 per cent of prostitutes by cultures on Thalmann's agar—a result which is certainly doubted by most observers.

Gurd (1908) cultivated gonococci in 55 cases out of 113 females suffering from vaginal discharges. Of these only 16 showed gonococci by microscopic examination of the smears. He considers therefore that in females at least the cultural method is superior. The microscopic diagnosis fails because of the relative scarcity of gonococci, and more especially on account of the presence of enormous numbers of other bacteria, many of which are Gram-negative. This renders detection of gonococci very difficult, so that negative results obtained from smears in females are not of much value.

He states that when the urethra or cervix is apparently the seat of an acute infection, the gonococcus is more easily isolated from these situations than from the vaginal discharge. In most cases, however, the vaginal discharge is sufficient, and usually of more value than that from either the urethra or the cervix. This despite the fact that many authors claim that the gonococci do not attack the vaginal mucosa itself.

He employed the following culture technique :—A small piece of absorbent cotton-wool wound about the end of a wire probe was used for obtaining the material. These swabs of course were sterilised and kept in sterile tubes. To obtain the vaginal secretion, the labia minora are held apart and the vaginal orifice cleansed with a sterile cotton sponge. Insert the swab into the vagina, and rub it thoroughly over the surface. It is essential that the mucosa be rubbed in order that the cells and fresher portions of the secretion in which viable organisms are found should be obtained.

In taking cultures from the urethra, the meatus is cleansed and the swab is passed into the urethra for a distance of 2 to 3 centimetres. Cervical and uterine discharges are obtained by exploring the cervix through a sterile bivalve speculum. The os is cleansed with a series of sterile cotton sponges. The swab is then passed into the opening and rubbed about against the mucosa of the cervix or uterus.

The material from the swabs is then planted directly upon slanted blood agar tubes or surface-seeded upon plates. A surface-seeding by the streak method is of great value, as it almost invariably isolates sufficient colonies for easy removal and for further examination. A little experience enables the examiner to make sufficiently sparse seedings upon slanted tubes. The direct seeding in this manner is more trustworthy than a preliminary suspension in broth or by ordinary plating methods from an emulsion of the material. As a rule, if the material is planted within six hours of its being obtained a good growth can be relied upon. The shorter the period, however, the better. The tubes and plates are then placed in the incubator and smears prepared from the swabs which have been moistened in the water of condensation.

Gurd prefers rubbing the swabs on the surface of the mucosa, and thinks that better diagnosis is thus obtained than by using only the fluid portion of the discharge.

Jadassohn (1910) states that in the vast majority of cases the microscopic examination by Gram's method is sufficient for the diagnosis. In cases, however, of unusual localisation, also in especially important cases, it is desirable to supplement the positive microscopic findings by cultural examination. If the microscope fails, then a culture is all the more necessary, where there are clinical grounds for suspicion, and where a definite diagnosis is especially required for forensic cases, or where marriage is contemplated. Of course, a negative culture should never induce one to omit a careful or thorough microscopic search.

Koch (1912) agrees with Jadassohn's opinions, and he considers that it is not a difficult procedure for an expert to verify the diagnosis by culture methods. Where the colonies of gonococci are scarce and mixed with numerous colonies of other bacteria, one must not jump to a diagnosis by macroscopic examination of the culture alone. It is necessary always to pick off the suspicious-looking colonies with a platinum loop, smear, stain with Gram, and examine microscopically in order to verify that the growth really consists of gonococci. Mistakes are very easily made if one attempts to make a diagnosis from the macroscopic appearance of the growth alone.

The opinion of the last two observers is more or less correct with regard to the diagnosis of gonorrhoea in the male, but it is hardly true in female cases. The author agrees with Gurd's opinion. The healthy adult vaginal secretion should contain a few epithelial cells, with Döderlein's bacillus. When pus cells appear, along with the presence of numerous bacteria and absence of Döderlein's bacillus, this indicates a pathological discharge. In all such cases an attempt should be made to diagnose or exclude gonorrhoea. This in the majority of cases is impossible by smear preparations and slope cultures. Where such numbers of organisms are present, the gonococcus in a slope culture has no chance of developing. It is overgrown and swamped, so to speak, by the overwhelming majority of other bacteria which grow more easily and more profusely. Two methods alone are capable of settling the diagnosis: (1) careful preparation of plate cultures; (2) the complement-fixation test.

The method of isolation by plate cultures is not only tedious but somewhat difficult,

and there can be no doubt that in all doubtful male and female cases the complement-fixation test will eventually be recognised as a valuable method of diagnosis.

The Tests for Determining when a Patient is Cured of Gonorrhœa. These tests of cure, which are often desirable in persons about to marry, are really the same as the diagnosis tests enumerated above.

Whitney, C. M. (1914), recommends ten different tests as follows:—(1) Microscopic examination of the discharge. (2) Instrumental examination of the urethra. (3) Urethroscopic examination. (4) Examination of the prostate and vesicles. (5) Alcohol test by drinking excess of alcohol. (6) The test by coitus. (7) Inducing a discharge by irritating antiseptics. (8) and (9) Bacteriological examination of the expressed vesicular and prostatic secretion by microscope and by culture. (10) The complement-fixation test.

Wolbarst (1915) gives a similar list of tests, but adds the cuti-reaction test. He states that should all of these tests prove negative repeatedly, the patient may be declared cured, but the physician cannot assume the full responsibility and guarantee of cure. The patient himself must assume that responsibility.

Herrold (1921) states that cultures of the prostatic and seminal fluid and first urine sediment, carefully collected, are the most reliable means of determining whether or not a gonorrhœa is cured. A good culture medium such as phosphate agar containing ascitic fluid or blood, and placed under partial oxygen tension, is necessary. Plates should be used instead of tubes. The complement-fixation and precipitin tests are also valuable, but the results should be taken in conjunction with the cultural findings. The pus cell content of smears and the macroscopic urinary appearances may be misleading, and by themselves constitute no safe index of cure.

Cattier (1921) cites Lebreton's study of the semen of persons supposed to be cured of gonorrhœa. Fully 80 per cent of those who had supposed themselves fully cured showed gonococci in the semen, examined within an hour. Cultivation of the seminal fluid is thus the best guarantee that the patient is not a carrier of gonococci. Cultivation of the secretions from the uterus at the beginning of menstruation may prove to be the best equivalent test in women. Unsuspected gonococcus infection of the urethra in the wife is one of the commonest causes of supposed "relapse" in the husband. He has had hundreds of instances of this.

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CHAPTER XIII

DIAGNOSIS OF GONORRHOEA (*continued*)

PSEUDO-GONOCOCCI—CULTURE DIAGNOSIS BETWEEN THE GONOCOCCUS, MENINGOCOCCUS, AND M. CATARRHALIS—OTHER GRAM-NEGATIVE ORGANISMS ALLIED TO M. CATARRHALIS

THE differential diagnosis in certain chronic cases of urethral gonorrhœa may present some difficulties, because of the occasional occurrence of other Gram-negative diplococci-pseudo-gonococci resembling the gonococcus.

Steinschneider and Galewsky (1889) found Gram-negative diplococci, like the gonococcus, in the male urethra on four occasions out of 86 cases, *i.e.* in 4.65 per cent. They were, however, always extracellular.

Finger, Schäffer, and Steinschneider (1894) found a Gram-negative diplococcus, which was not the gonococcus, in only 4.6 per cent of cases in a large series.

v. Hoffmann (1904) out of 62 cases demonstrated Gram-negative diplococci like the gonococcus on two occasions, Gram-negative streptococci on one occasion, and Gram-negative staphylococci on three occasions.

Pfeiffer (1904) found a Gram-negative diplococcus in one case out of 24 healthy male urethrae.

Noguès and Wassermann (1899), Johnston, v. Zeissl (1903), and Dreyer (1904) have grown similar micro-organisms from cases of urethritis.

Tuttle and also Hogge (1893) obtained Gram-negative pseudo-gonococci in cases of cystitis. Hogge found that they took longer to decolorise by Gram's method than the true gonococcus. Finger (1905) described a bacillus in gonorrhœal urethritis which often formed short chains. It often remained unstained in the middle, and thereby appeared like a diplococcus. Hammer (1895) found a short thick diplococcus. Kiefer (1895) observed especially in women a short Gram-negative diplobacillus which was often intracellular, also a bacillus which assumed pleomorphic shapes, some forms resembling diplococci. Galli-Valerio obtained Gram-negative pseudo-gonococci from the epididymis and joints, and Petersen obtained similar diplococci from a tubo-ovarian abscess.

Baermann (1904) succeeded in cultivating a gonococcus-like germ in 12 cases from the cervical secretion. The same type of diplococcus was found in the rectal discharge of a man, and the condition was erroneously diagnosed as gonorrhœa on the strength of a microscopic examination of a smear.

In cases therefore where isolated Gram-negative diplococci are found without any evidence of the characteristic grouping of gonococci, and where intracellular forms are absent, it is dangerous to give a definite diagnosis from a microscopic examination of the smear alone. Even in some rare cases these non-pathogenic diplococci have been found actually within the pus cells, but usually an expert can distinguish them by their size and shape, and as a rule they decolorise more slowly than the gonococcus.

Gurd (1908) made cultures and smears from the female genitals in 113 cases, comprising 105 cultures from the vagina, 28 from the urethra, and 17 from the cervix. Most

of the cases examined were gonorrhœal or suspected chronic cases. In four cases he isolated by culture the *Micrococcus catarrhalis*. In two cases diplococci of the *Micrococcus pharyngis* type were obtained, and in one case he got a large Gram-negative diplococcus which he calls the *Diplococcus magnus* of Rosenthal.

Kutscher, *vide* v. Stabsarzt and Kutscher (1909), examined 67 cases of chronic gonorrhœa, microscopically and culturally, with regard to the occurrence of these so-called "pseudo-gonococci." The pus examined was taken from the following localities :—

- 47 cases from the urethra.
- 8 cases from the vagina.
- 4 cases from the cervix.
- 1 case from the Bartholin's glands.
- 5 cases from the prostate.
- 1 case from the para-urethral glands.
- 1 case from Cowper's gland.

Out of the 67 different samples examined he found a Gram-negative diplococcus resembling the gonococcus in only one by microscopic examination. This sample was derived from the female urethra. The diplococci were extracellular. They decolorised more slowly than the gonococcus, and isolated pairs remained Gram-positive. On the other hand, he found in 44 cases (65·4 per cent) the short Gram-negative diplobacillus described by various authors. This germ was obtained chiefly from the female vagina and urethra, but it also occurred in the male. They often occurred in large numbers. Certain short involution forms of this diplobacillus could easily be confused with gonococci, but as a rule they are more elongated in shape than the latter.

Wormser (1910) drew attention to a Gram-negative coccus—the *Micrococcus fallax* described by Rousseau (1905). He thinks that this coccus may be responsible for the continuance of chronic urethritis after gonorrhœa. It is a kidney-shaped diplococcus, lightly encapsulated, and occurs in masses both intra- and extracellular. In smears it is always Gram-negative, but tends to be slightly Gram-positive in cultures. It grows at 20° C. to 41° C., but the optimum temperature is 37° C. When injected into guinea-pigs it produces abscesses, but it can be inoculated into the human urethra without producing any lesions. The organism is somewhat larger in size than the gonococcus. Wormser succeeded in isolating it from cases of vulvo-vaginitis in young females, and from purulent ophthalmia as well as from the urethra. (See also chapter on Non-gonorrhœal Urethritis.)

According to more recent observations the meningococcus can also be obtained on rare occasions from the male and female genital tracts.

Martin (1910) states that it can frequently be isolated from the urine in cases of cerebro-spinal meningitis. Its differentiation from the gonococcus is not possible by microscopic examination of smears, because of its intracellular position, its characteristic grouping, and its coffee-bean shape.

Schottmüller (1905) repeatedly observed a meningococcal epididymitis as a complication of cerebro-spinal meningitis.

Reuter (1905) reported on a case of cerebro-spinal meningitis with a purulent peri-orchitis, in a youth nineteen years old. In this case he cultivated the meningococcus from the cerebro-spinal fluid, and also from the pus obtained from the testicle.

Pick (1907) records a case of meningococcal infection of the seminal vesicle of a young man eighteen years old, which had come from a meningitis by way of the blood stream. A careful bacteriological investigation showed that the semino-vesiculitis had really in this case arisen from a metastasis of the meningococcus. There was no evidence of any acute or chronic gonorrhœal process in the whole of the remaining genital tract. According to the investigations of Zupnik (1906) inoculation of meningococci into the urethra is not capable of calling forth a purulent inflammation of the urethral mucous membrane. He experimented in five different cases.

EXPLANATION OF PLATE IV

No. 1.—Culture of large Gram-negative diplococcus (*Diplococcus magnus* of Rosenthal?) from chronic urethral discharge. Glucose-plasma agar. Nat. size.

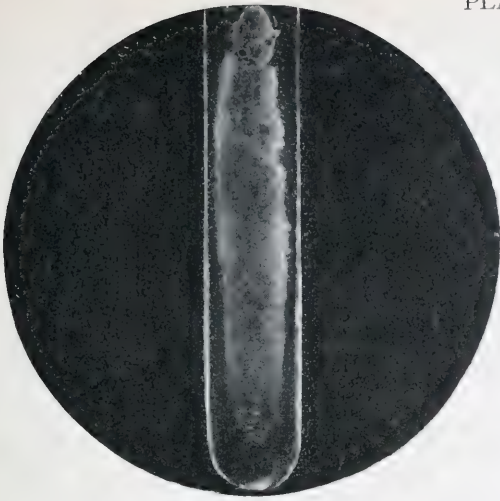
No. 2.—Smear from culture tube No. 1, stained Gram. Note the large size of this diplococcus as compared with the gonococcus in microphoto. No. 4. Magnified 1000 diameters.

No. 3.—Culture of the gonococcus on glucose-plasma agar. Nat. size.

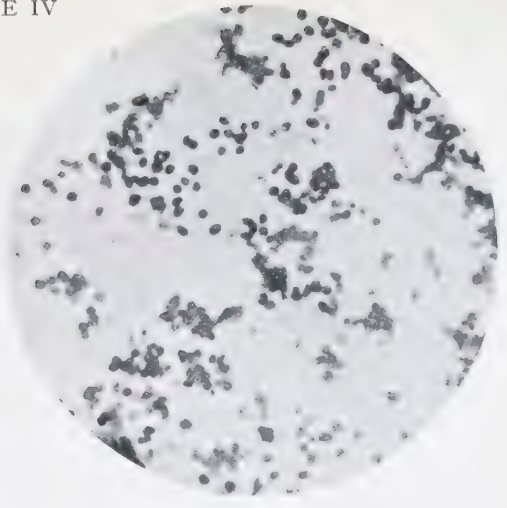
No. 4.—Smear from culture tube No. 3, stained Gram. Note the small size of the gonococci compared with the pseudo-gonococci in No. 2. Magnified 1000 diameters.

No. 5.—Culture of the gonococcus on glucose-plasma agar. (Seven-days-old culture.) Nat. size.

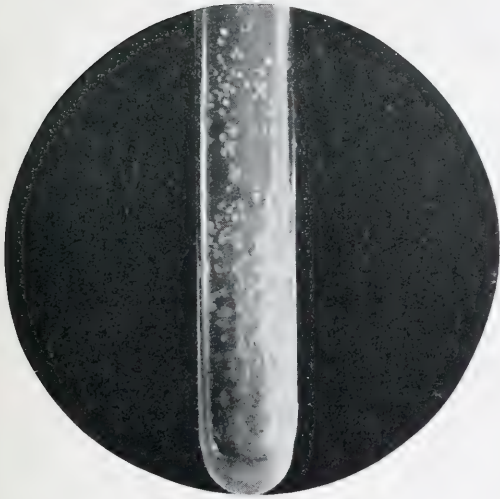
No. 6.—Smear from culture tube No. 5, stained Gram. Note that the gonococci have undergone autolysis. Magnified 1000 diameters.



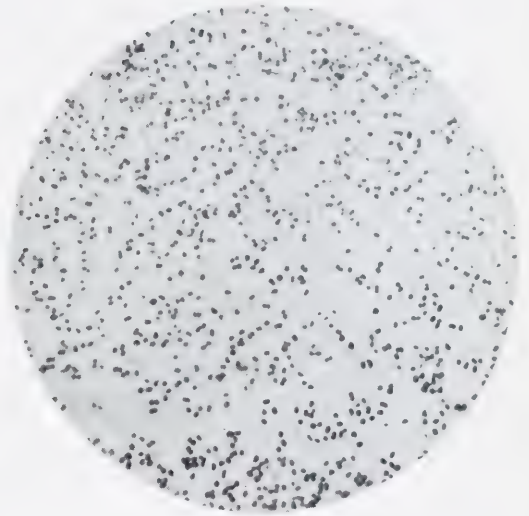
No. 1.



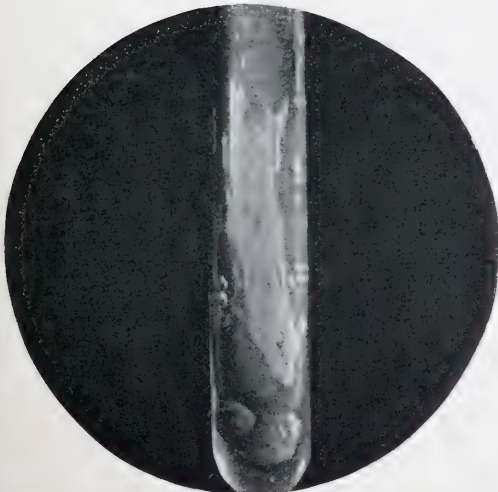
No. 2.



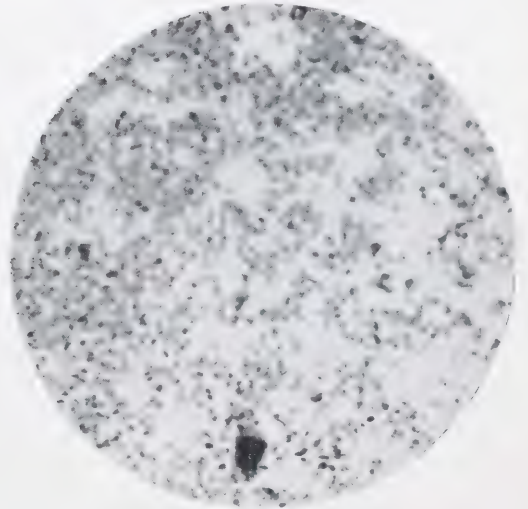
No. 3.



No. 4.



No. 5.



No. 6.

Norris (1913) states that meningococci are present occasionally in the female genital tract, and that they may produce ophthalmia.

In differential diagnosis one must bear in mind those cases of cerebro-spinal meningitis with complications at the site of the genital tract. On the other hand, there are cases on record where the central nervous system and its membranes were attacked by a general gonococcal infection. There is also the possibility that cerebro-spinal meningitis and gonorrhoea may occur simultaneously.

Rothe (1908) considers that in cases where there is a systemic infection with endocarditis and joint affections it might be wise to make a differential diagnosis between the meningococcus and the gonococcus by cultural methods.

The differential diagnosis in cases of extra-genital gonorrhoeal affections of the mucous membranes, as, for example, in gonorrhoeal conjunctivitis, may be very difficult. This difficulty is due to the fact that other Gram-negative diplococci resembling the gonococcus are frequently found in the conjunctival secretion. Morax (1894), Abelsdorf-Neumann (1900), Krukenberg, Urbahn (1901), Axenfeld (1899-1901), and Brons (1907) showed that *M. catarrhalis* can occur in the conjunctiva. It is also known from the extensive researches carried out in cerebro-spinal meningitis that various species of Gram-negative diplococci (*Diplococcus flavus*, *siccus*, *cinereus*, etc.) can migrate from the nasopharynx through the nasal canal into the lacrymal sac; *vide* Kutscher (1907).

The researches of Schmitt, Thomsen, Robinson, and Brons (1907) have shown that the meningococcus can occur in the conjunctiva, and that it is impossible to distinguish this organism from the gonococcus in the conjunctival pus. The microscopic diagnosis in such circumstances is directly impossible, because both the meningococcus and *M. catarrhalis* lie stored within the leucocytes, exactly resembling gonococci. In such cases of catarrhal inflammation of the conjunctival mucous membrane Kutscher advises diagnosis by cultural methods, more especially where the gonorrhoeal aetiology cannot be established clinically by the coexistence of a genital gonorrhoea.

Again, in cases of general metastatic gonorrhoeal infections it is necessary to verify the nature of the cocci by culture. In general infections the meningococcus, as already stated, can produce an illness almost identical, *viz.* endocarditis, joint affections, and symptoms of a general septicæmia, and even septic pyæmia. According to Kutscher the clinical picture produced by a septic metastasis due to the meningococcus corresponds in an extraordinary way with that produced by the gonococcus. This similarity may be even more striking where, as sometimes occurs, the symptoms of meningitis are absent.

Marcovich (1906) and Jakobitz (1907) have reported on several such cases.

Schottmüller (1905) saw an ulcerative endocarditis as a result of a meningococcal infection without meningitis.

Prochaska (1905) and de Josselin de Jong (1907) described inflammation of the meninges as a complication of a gonorrhoeal infection.

Again, it is worth noting that the *Micrococcus catarrhalis* produces very rarely a general infection. But the differential diagnosis with regard to this organism is more frequently required in infections of the lungs in children in acute bronchitis and broncho-pneumonia; *vide* Frosch and Kolle (1896) and Ghon and Pfeiffer (1902).

Culture Diagnosis between the Gonococcus, Meningococcus, and Micrococcus catarrhalis, etc.—(a) *Power of Growth.* Koch (1912) states that on a suitable culture medium such as ascitic agar, meningococcus cultures after twenty-four hours' incubation at 37° C. show colonies with an average diameter of 2 to 3 mm. The gonococcus colonies, on the other hand, seldom exceed a diameter of from 1 to 1.5 mm. with the same period of incubation. In other words, the meningococcus grows much more profusely and strongly than the gonococcus; *vide* Flexner (1907). This is also the experience of the author with regard to human plasma agar.

Martin (1910) states that the meningococcus grows more profusely than the gonococcus. It is more prone to autolysis, but less susceptible to cold and less sensitive to reaction.

He found it capable of growing at any reaction from slight alkalinity to litmus, to +15 acid to phenolphthalein. Moreover, it is much more easy to subculture the meningococcus on to ordinary media, and even primary isolations are possible on ordinary agar. Pollock and Harrison (1912) state that the meningococcus is less sensitive to changes in temperature and reaction, that it grows more rapidly on serum agar, and the colonies are more opaque than in the case of the gonococcus, and it can generally be cultivated on plain nutrient agar. The *Micrococcus catarrhalis* as a rule grows more profusely and more easily than the meningococcus. Growths can be obtained on ordinary agar, and it can even develop on gelatin (without liquefaction) at room temperature. Some strains, however, will not grow on ordinary agar or gelatin until they have been subcultured for several generations on serum agar. As a rule it lives for a considerable time at room temperature, but some strains may die out as readily as the meningococcus. The range of reaction, as in the case of the meningococcus, is a wide one. This organism is never pigmented, and as a rule it is larger in size than the gonococcus.

(b) *Appearance of Growth*.—The gonococcus growths show a greyish, bluish, white, moist transparent appearance. If the growth is very thick and profuse, as on human plasma agar, it may show a slightly yellowish tinge.

The meningococcus growth shows much the same greyish-white appearance, except that it is obviously thicker and more profuse.

The *M. catarrhalis* is more inclined to grow in separate colonies each of which is markedly raised and beady in appearance. The growth is not so transparent and not so moist.

(c) *Microscopic Appearance of the Colonies*.—When the growths are examined with the low power of the microscope, it can be observed that the gonococcus colonies have almost without exception a scalloped margin, and often excrescences project out from the marginal zone. The margin is definitely transparent and smooth, whereas the centre is raised, granular, opaque and yellowish. Moreover, they show concentric and radial striations (see Plate II., Nos. 3 and 4).

The colonies of the meningococcus appear as flat homogeneous discs, with, as a rule, smooth, delicate, almost invisible, occasionally very slightly wavy, but never definitely scalloped margins; *vide* Kutscher (1907). According to this author the cultural features suffice to distinguish the meningococcus from the gonococcus, and it is unnecessary to employ agglutination and complement-fixation tests in differential diagnosis.

The *M. catarrhalis* colonies are markedly different. They have an opaque, white varnished appearance, and stand up definitely from the surface of the medium. Later their margins become somewhat crenated.

(d) *The Alkali Test*.—This has already been described by the author in Chapter IX.

(e) *The Emulsion Test*.—The gonococcus and the meningococcus break up very readily into a uniform emulsion when shaken up in saline with glass beads. The meningococcus is perhaps more viscid than the gonococcus, as it autolyses more readily.

The *M. catarrhalis* is extremely difficult to emulsify; even after prolonged shaking many colonies remain incompletely disintegrated. The colonies stick tenaciously to the medium, and are difficult to pick off with the platinum loop. It does not autolyse so readily as the other two.

(f) *The Sugar Fermentation Tests*.—See Chapter IX.

Other Gram-negative Organisms allied to the *Micrococcus catarrhalis*.—Five species of Gram-negative cocci resembling *M. catarrhalis* have been found in the respiratory tract by v. Lingelsheim (1906).

These are liable to be confused with the gonococcus, as they sometimes occur in the nasal passages and in the conjunctival secretion. They are easy, however, to differentiate from the gonococcus, by cultural methods, by the definitely different appearance of the colonies, and by their different sugar reactions. They differ from the true *M. catarrhalis* in pigment production, in agglutination, and in fermentation reactions.

v. Lingelsheim applied to these species the following names :—

- (1) *Micrococcus pharyngis siccus*—yellowish tint, and adheres very firmly to the medium.
- (2) *Micrococcus pharyngis cinereus*—greyish-white.
- (3) *Diplococcus pharyngis flavus I.*—greenish-yellow.
- (4) *Diplococcus pharyngis flavus II.*—golden yellow.
- (5) *Diplococcus pharyngis flavus III.*—light yellow.

He also described the *Diplococcus mucosus*, which possesses a capsule and can be distinguished by a capsular stain. It grows in a manner similar to the meningococcus.

Gordon (1905) had also noticed the occurrence of atypical fermenters in the catarrhalis group, and described three varieties. v. Lingelsheim and Gordon (1905) give the following fermentation tables :—

VON LINGELSHEIM

Organism.	No. of Strains Tested.	Dextrose.	Lævulose.	Galactose.	Mannite.	Dulc. ite.	Saccharose.	Maltose.	Lactose.	Inulin.
<i>Meningococcus</i>	83	+	o	o	o	o	o	+	o	o
<i>M. catarrhalis</i>	21	o	o	o	o	o	o	o	o	o
<i>M. cinereus</i>	4	o	o	o	o	o	o	o	o	o
<i>Dip. pharyn. flav. I.</i>	6	+	+	o	o	o	o	+	o	o
.. .. II.	4	+	+	o	o	o	o	+	o	o
.. .. III.	8	+	o	o	o	o	o	+	o	o
.. .. siccus	4	+	+	o	o	o	o	+	o	o

GORDON

Organism.	No. of Strains Tested.	Dextrose.	Galactose.	Saccharose.	Maltose.	Growth on Gelatin at 20° C.
Catarrhalis group	22	=	=	=	=	+
2 from { I	from { I	+	+	+	+	o
urine { I	urine { I	+	-	-	+	+
<i>Meningococcus</i>	1	+	+	=	+	o
<i>Gonococcus</i>	1	+	+	=	=	o

Elsler and Huntoon (1909) divided the chromogenic Gram-negative cocci of the nasopharynx into three groups.

Group I. types produced acid in dextrose, maltose, lævulose, and saccharose, but differed in agglutination reaction.

Group II. fermented dextrose, maltose, and lævulose, and apparently were the same as v. Lingelsheim's *Diplococcus pharyngis flavus I.*

Group III. differed only in minor inconstant features from those of chromogenic Group I.

Martin (1910) found that none of the catarrhalis group liquefied gelatin, and that some did not grow at room temperature.

Gurd states that *M. catarrhalis* does not coagulate milk.

Elsler and Huntoon (1909) give the following table of fermentations :—

Organism.	No. of Strains Tested.	Dextrose.	Maltose.	Laevulose.	Saccharose.	Lactose.	Galactose.
Meningococcus . . .	200	+	+	o	o	o	o
Pseudo-meningococcus	6	+	-	o	o	o	o
Gonococcus . . .	15	+	o	o	o	o	o
M. catarrhalis . . .	64	o	o	o	o	o	o
M. pharyngis siccus . .	2	+	+	+	+	o	o
Chromogenic Group I.	28	+	+	+	+	o	o
" " II.	11	+	-	+	o	o	o
" " III.	9	+	+	o	o	o	o
Jaeger meningococcus (Kral) . . .	1	+	+	-	+	+	-
Diplococcus crassus (Kral) . . .	1	+	-	+	+	+	+

The following table on the chief characteristics of six Gram-negative cocci by Dunn and Gordon (1905) may be found useful:—

Organism and Source.	Growth on Nutrose Ascitic Agar.	Growth on Gelatin at 20° C.	Pathogenicity.	Action on Carbohydrates. + = Acid. - = Alkali. o = No reaction.			
				Glucose.	Galactose.	Maltose.	Saccharose.
M. catarrhalis from nasal and pharyngeal discharge	Opaque, granular	Grows on gelatin at 20° C. Ord. agar at 37° C.	Mice and guinea-pigs by intraperitoneal inoculation only	-	-	-	-
Meningococcus C.—spinal fluid	Clean, smooth	Negative	Mice and guinea-pigs in some cases by intraperitoneal inoculation	+	+	-	-
Gonococcus	No growth unless blood added	Negative	Ditto	+	+	o	o
Nasal discharge influenza-like epidemic	Clear, smooth, and becomes yellowish	Negative at first, later positive Ord. agar at 37° C.	Mice and guinea-pigs by intraperitoneal injection	+	-	+	-
From urethra	Opaque, granular	Negative	Ditto	+	+	+	+
M. melitensis	Creamy and slightly yellowish	Positive	Monkeys, rabbits, and guinea-pigs by intracerebral inoculation	-	o	o	o
Malta fever							

The *M. melitensis* is often found in the urine of Malta fever patients.

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CHAPTER XIV

THE SECONDARY ORGANISMS FOUND IN CHRONIC GONORRHOEA

INTRODUCTORY—NORMAL FLORA OF MALE AND FEMALE GENITAL TRACTS—SECONDARY ORGANISMS IN GONORRHOEAL INFECTIONS OF GENITAL TRACT—SECONDARY ORGANISMS IN METASTATIC INFECTIONS—ORGANISMS FOUND IN VENEREAL WARTS

THE last chapter has dealt only with the non-gonococcal Gram-negative diplococci which may occur in gonorrhœa and thereby complicate the diagnosis. Besides these, however, there occur, more especially in *chronic* gonorrhœa of the genital tract, a whole host of secondary organisms. The latter, being quite different from the gonococcus in appearance and staining, are hardly likely to interfere much with the diagnosis; nevertheless, they must be regarded as of considerable importance. Professor John Chiene at Edinburgh University used to tell his students that "the gonococcus is a typical Scotsman. It is a pioneer, a colonist, which settles down and renders the soil suitable for other breeds to follow." Whether the simile is a good one or not, it is nevertheless very true that the secondary organisms are not generally capable of settling down in the urethra and the genito-urinary tract unless the mucous membrane has been devitalised or damaged. In very early recent cases of gonorrhœa the infection is practically always found to be purely gonococcal, and pure cultures of this organism can often be obtained from the pus. Later, however, when the mucous membrane has been congested and ulcerated, other organisms such as staphylococci, diphtheroids, etc., are able to gain a footing, so to speak, and may penetrate into the urethral glands and even into the prostate itself. Later, when the gonococcus is destroyed these secondary germs continue to multiply in the follicles and prostate, and may be then responsible for a low chronic form of urethritis which is often very persistent, though the only symptoms may be a few urinary shreds and a muco-purulent bead in the morning.

In the author's opinion chemical injections and irrigations are chiefly responsible for these secondary infections. Most of the organisms concerned are saprophytic and inhabit the prepuce, glans penis, and the fossa navicularis. Irrigations and injections drive them farther up, and give them an opportunity for settling down on the surface devitalised by the gonococcus. Experiments carried out by Dr. Lees and by the author have demonstrated that cases which are purely gonococcal will generally remain such so long as irrigations and injections are avoided. Immediately, however, that the latter are commenced, secondary organisms appear in the discharges, and continue there after this treatment has ceased. When, however, the irrigation and injection treatment was carried out like an aseptic operation, it was observed that secondary infections did not occur in the majority of cases. In treatment, therefore, the uro-genital tract should be guarded almost as carefully as a knee-joint which has been opened aseptically, and the greatest care should be used to keep out ordinary saprophytic and pyogenic organisms.

Some years ago the author had a very striking demonstration of the evil effects that may arise from unskilled injections per urethram, even in non-gonococcal cases. An

officer reported at the out-patient department of Rochester Row Military Hospital with a urethral discharge, strangury, and frequent micturition. His prostate was markedly enlarged and tender and the urine contained large numbers of shreds. The penile urethra was found to be unaffected. The shreds consisted of pus cells containing enormous numbers of large staphylococci, and cultures showed a pure growth of this organism. No gonococci could be found by smear or culture, and the complement-fixation test was completely negative.

The history was that, after connection three weeks previously, he had injected himself frequently with a lysol solution for prophylactic reasons. Evidently the solution was over-strong and irritating, staphylococci had been driven up the urethra and had settled down in the prostate, causing an acute staphylococcal prostatitis.

In this case the patient himself was to blame, but unfortunately the physician and surgeon, even in these days of aseptic surgery, are sometimes at fault. No irrigation, no injection, and no instrument whatsoever should be admitted into the urethra, except under most rigid aseptic precautions. Not only must the instruments, nozzles, and fluids be sterile, but also the glans penis and the lips of the urethral orifice must be thoroughly cleansed, preferably with weak spirit solution.

The author is also antagonistic to the use of strong antiseptic irrigations and injections. The gonococcus is very easily killed with weak antiseptics. Very strong solutions are not only superfluous but harmful, because they injure, congest, and devitalise the mucous membrane and make it more susceptible to the ravages of all kinds of germs.

The gonococcus, of course, is undoubtedly the germ which causes the greatest damage to the genito-urinary tract, and compared with it the damage caused by secondary organisms falls somewhat into the background. This is the reason of their neglect, and many are inclined to regard their presence as a matter of course. Moreover, in the post-gonorrhœal conditions where there is only a muco-purulent morning drop in which no gonococci can be found, where perhaps the complement-fixation test is negative, and at any rate where there is strong evidence that the case is free from gonorrhœa, some physicians regard the patient as non-infectious and safe to marry. Kidd (1917) is inclined to the belief that such cases where secondary organisms alone are present in the scant discharge are non-infective. The author, although willing to grant that such cases are not particularly dangerous, is nevertheless of the opinion that danger does exist. At any rate no bacteriologist would consider the constant deposition of quantities of staphylococci, diphtheroid bacilli, etc., in and around the orifice of the cervical canal in the female as a harmless act. Moreover, the author has been very forcibly impressed with the marked similarity of the flora occurring in chronic gonorrhœa in the male with the corresponding flora in chronic gonorrhœa of the female. Moreover, in females with leucorrhœa and septic discharges which are considered non-gonococcal, the organisms which are found are again identical with those which occur in the muco-purulent morning drops of the male. These observations must lead one to suspect that the unhealthy flora of the two sexes is interchangeable as well as the gonococcus, and for this reason the author is unable to regard even a chronic "morning drop," however free from gonococci, as safe and harmless.

Before passing to the study of the secondary organisms found in chronic gonorrhœa, it is advisable to consider the normal flora of the male and female genital tracts. It is very difficult to draw a hard and fast line of demarcation between the normal flora and the pathological flora, more especially in the female. During health, certain types of organisms which may be called saprophytic lurk about the uro-genital passages. When, however, the mucous surface is inflamed and damaged by the gonococcus, these more or less saprophytic organisms multiply to an enormous extent and gain a hold on the congested mucosa. When this occurs they play a considerable rôle in the aggravation or continuance of the disease, and must be regarded as no longer saprophytes, but as definitely pathological germs.

Indeed, long after the disappearance of the gonococcus, these secondary organisms,

having become established in the mucous glands, may be responsible for a post-gonorrhoeal folliculitis, with a persistent, though mild form of gleet.

The Normal Flora of the Male Genital Tract.—Certain types of organisms found in the urethra of healthy persons have already been mentioned in Chapter XIII. In health, however, this tract in the male is generally sterile. If the external urinary meatus is thoroughly cleansed with alcohol, and the urine is passed into a sterile flask and then centrifuged in a sterile tube, the deposit should yield no growth when inoculated on to a culture medium. When this technique is carefully carried out it will often be found that with normal persons the culture tube will remain sterile. On the other hand, the growth of a few colonies of staphylococci, diphtheroid bacilli, or pneumococcus-like organisms, by no means denotes a diseased condition, since even after careful cleansing of the meatus the urine of healthy persons will at times yield such growths.

No doubt these organisms have come from the portion of the urethra near to the meatus, just where the alcohol cleansing has failed to reach them. If they actually exist in numbers farther up the urethra, then that urethra cannot be considered as normal or healthy.

The posterior urethra, the prostate, all glands, and the bladder should in health be free from organisms.

With regard to the glans penis and the mucous surface within the foreskin, organisms are always present in small or large numbers according to the cleanliness or dirtiness of the individual. The germs which are most commonly found are staphylococci, diphtheroid bacilli, a species of pneumococcus or enterococcus, and the smegma bacillus. The greater the cleanliness, the more scarce will these organisms be. Spirochætes of the refringens and gracilis type may be found in this locality, but not if cleanliness is maintained.

Eyre and Stewart (1909) state that *B. xerosis*, embracing several varieties of diphtheroid bacilli, is frequently met with in the healthy urethra.

Noguchi (1918) states that three species of spirochætes are found in the normal male genitalia, viz. *Spirochæta refringens*, *Treponema calligyrum*, and *Treponema minutum*. *T. calligyrum* is the commonest and resembles an atypical *T. pallidum*. *T. minutum* is smaller than pallidum with a larger number of shallower spirals in proportion to its length, and many short forms are seen such as are never found with *T. pallidum*.

The Normal Flora of the Female Genital Tract.—What has been said with regard to the male urethra should apply more or less to the female urethra. With regard to the vagina, however, the normal flora is not so simple and well defined. It is very difficult to state definitely the amount and variety of organisms which inhabit the healthy vagina, and what indicates the beginnings of a pathological flora, but a certain amount of information is at hand. Generally speaking, it may be stated with truth that the smaller the number and variety of organisms present in this mucous-lined channel, the greater is its state of health; and *vice versa*, the greater the number and variety of organisms present, the more abnormal and unhealthy is its condition. With regard to the upper part of the cervical canal, the uterus, Fallopian tubes and ovaries, these normally should contain no organisms whatsoever, so that the presence of germs in these localities indicates always an unhealthy or pathological condition.

The external genitals (vulva, labia, etc.) must, of course, always harbour normally a small or large number of organisms such as staphylococci, diphtheroids, *B. coli*, etc., according to the state of cleanliness.

(a) *The Normal Flora of the Infant Vagina.*—Vahle states that the vagina in a child is sterile for the first twenty-four hours after birth, but that it is inhabited by staphylococci and streptococci about the third day.

Stroganoff reports that organisms (staphylococci, streptococci, diplococci, etc.) may sometimes be found a few hours after birth, and in some cases the inoculation occurs during birth and even *in utero*.

Schmidgall examined the vaginal flora in 21 infants and 10 children in the first year of life. He found staphylococci, streptococci, bacillus coli communis, and vaginal bacilli. Occasionally Gram-negative coliform bacilli, micrococcus tetrigenus, saccharomyces, anaerobic streptococci, bacillus hamophilus, and bacillus bifidus were present. He states that the vagina becomes infected with intestinal bacteria in the first nine days of life, and that these form about half of the germs present in older children. He does not consider that the vagina has any marked natural antiseptic power.

(b) *The Normal Flora of the Adult Vagina*.—Bumm (1885) described two Gram-positive diplococci :—

(1) *Diplococcus albicans amplius*, which he isolated from the normal lochia. It is larger than the gonococcus, liquefies gelatin, and grows fairly profusely in greyish-white colonies.

(2) *Micrococcus subflavus*, isolated from the lochia and urethra of healthy women. Grows slowly on all media, producing yellowish-brown colonies. Liquefies gelatin slowly. It has no deleterious action on the mucous membrane, but produces an abscess when injected into the cellular tissues.

Döderlein (1892) was apparently the first observer to describe the so-called vaginal bacillus. It is usually present in considerable numbers in all normal adult females. It is a long, thick, Gram-positive, non-motile, anaerobic bacillus, and it produces lactic acid. By virtue of this production of lactic acid it is supposed to inhibit the growth of other organisms such as staphylococci, etc. In an examination of 195 normal cases he found a yeast fungus—*Monilia candida bonorden*—in 36 per cent, and streptococci in 4 per cent. Some of these streptococci were virulent. Other observers have found streptococci in a much higher percentage of cases.

Waltherd (1894) stated that the vestibule, the vagina, and the lower part of the cervical canal were normally septic, but that the upper part of the cervical canal, the uterus, and tubes were sterile.

Gurd (1908) found, as a rule, in the normal adult vagina—

- (1) Döderlein's vaginal bacillus, Gram-positive, occurring in pairs or threes.
- (2) A Gram-positive bacillus of the xerosis diphtheroid type.
- (3) A small Gram-negative bacillus, often short and fat and occurring in pairs, and consequently liable to be confused with the gonococcus.

He states that the discharge from a healthy vagina contains, as a rule, a small number of pus cells, a large number of epithelial cells, together with a small amount of mucus. As a rule a small number of other organisms along with the presence of numbers of Döderlein's bacillus is suggestive of a healthy condition of the vagina.

Shaw (1917) states that *Saccharomyces albicans* occurs frequently in the vagina in combination with other organisms.

Foulerton and Bonney (1905) state that a diphtheroid bacillus is a common inhabitant of the non-pregnant cervix.

Corbus (1913) found that the vaginal secretions of 100 normal women showed bacteria and spirochaetes similar to those found in the smegma of the male, but he did not find spirochaetes such as are found in balanitis.

According to Noguchi and Kaliski (1918) the spirochaetal flora of the normal female genitalia is similar to that of the male and consists of *Treponema calligyrum*, *Treponema minutum*, and *Spirochaeta refringens*. *T. calligyrum* usually predominates and *refringens* is least frequent. The female genitalia are generally much richer in the number of spirochaetes than the male.

(c) *The Normal Flora of the Vagina during Pregnancy*.—Krönig (1894) maintained that the vaginal secretion of pregnant women was strongly antagonistic to germs. This antagonism is due, according to Menge, to the acid products of the normal flora, to the acidity of the secretions, and also due to leucocytes, phagocytosis, and the presence of free oxygen.

Stroganoff found bacteria in the vaginas of all pregnant women. The vaginal bacillus of Döderlein was the most common type. He maintained, however, that no hard-and-fast line could be drawn between the flora of normal and pathogenic cases.

Walthard (1894) found streptococci in 27 cases out of 100 during pregnancy. The streptococci did not cause death when injected into animals, and he concluded therefore that they were non-pathogenic types. He found after delivery in some of his 100 cases, staphylococci, bacillus coli, and gonococci. He was not dealing, therefore, with cases which were entirely normal.

Williams (1898) published an article in which he gives the cultural results obtained in 92 cases of vaginal secretion from healthy women.

In 54 the plates remained absolutely sterile. Cocci occurred only in 12, 9 of which were non-pathogenic. The three pathogenic cocci isolated by him were the staphylococcus epidermidis albus, twice, and an anaerobic streptococcus, once. He therefore supported Krönig and Menge, and gave his opinion against the idea of auto-infection and against the prophylactic douche in maternity cases.

Duhressen, by a series of experiments made by introducing cultures of staphylococcus, streptococcus, *B. pyocyaneus*, and gonococcus, into the vagina of healthy adults, demonstrated that this organ had the power in these cases of sterilising itself. He stated that in forty-eight hours he was unable to recover the organisms.

Edgar (1904) obtained from the vagina in 20 normal cases the staphylococcus pyogenes albus in 8, the staphylococcus aureus in 3, and the streptococcus pyogenes in 1. He quotes various authors, notably von Rosthorn and Lenhartz, to show that the vagina is by no means always sterile, and that the vaginal secretion possesses no inherent bactericidal power. Edgar therefore favours the possibility of auto-infection, and thinks that ante-partum douches may do good. In this respect is quoted Hofmeier, who uses the douche, and has the smallest mortality of any maternity clinic in Germany, namely, .067 per cent.

Gonnet (1906) examined 100 cases. He found a streptococcus which he called gracilis in 16 cases, and which he believed to be non-pathogenic. He was not successful in isolating the streptococcus pyogenes from any case.

The Secondary Organisms found by various Observers in Gonorrhœal Affections of the Uro-genital Tract.—Bumm (1885) obtained from gonorrhœal pus a *Micrococcus citreus conglomeratus* which was Gram-positive. It was easily cultivated and presented a moist, shiny, unwrinkled growth. It liquefied gelatin. He observed that this organism was also present in the air and that it was non-pathogenic. He also described a *Diplococcus albicans tardissimus* obtained from gonorrhœal discharges. The growth was greyish-white, and in old colonies the surface was wrinkled. The germ was Gram-positive and did not liquefy gelatin.

He described five kidney-shaped intracellular diplococci, one Gram-positive and the other four Gram-negative, which could only be distinguished from the gonococcus by culture.

Gurd (1908) investigated 113 female cases. Twenty of these showed no evidence of an inflammatory condition; 61 were gonorrhœal, and 32 were doubtful.

He gives the following table of his cultural findings :—

Organisms Obtained.	Gonorrhœa.			Negative to Gonorrhœa.	Totals.
	Acute.	Subacute.	Chronic.		
Gonococci	8	20	1	15	44
Gonococci ?	2	6	..	8
M. catarrhalis	4	..	4
Other Gram-negative cocci	3	..	3
Pneumococci	2	3	5
Streptococci	1	1	1	2	5
Staphylococcus albus	Staphylococci of various kinds always present.				
„ epidermidis					
„ aureus					
„ rosaceus					
„ citreus, etc.					
B. Coli	3	2	9	4	18
Vaginal bacillus (Döderlein)	3	5	8
Saccharomyces	1	1	2
Diplobacillus vaginæ " Influenzoid "	Usually found in old cultures.				

He also examined a total of 350 smears, and states that in acute cases of gonorrhœa there is a copious discharge of pus from the vagina with enormous numbers of large and small Gram-negative bacilli and Gram-positive cocci. In chronic cases there are numerous epithelial cells filled with cocci and bacilli of all kinds. As many are present within the epithelial cells as within the pus cells. He describes the following organisms in detail:—

(1) *Pneumococcus*.—Found frequently, more especially in acute inflammatory conditions. All fermented inulin, with a production of at least 1·5 per cent acid (cold titration) when grown on sugar-free inulin broth.

(2) *Diplobacillus vaginæ*.—A short fat Gram-negative non-motile bacillus 1·5 to 2 μ in length and 0·8 μ broad. Lanceolate shaped, and occurs in pairs with the broad ends together. In cultures it occasionally occurs in short chains of 4 to 6. It grows on blood agar 0·6 per cent acid in the form of fine raised transparent colonies, not more than 0·5 mm. in diameter. The growth is granular and difficult to emulsify. Does not grow on plain agar, and only scant growth on glycerine agar. It is non-pathogenic, does not affect laboratory animals, but it is liable to be confused with the gonococcus in smears.

(3) *Influenzoid bacillus*.—This is an extremely small Gram-negative bacillus. It grows with difficulty, and only on blood agar. Gurd states that it is usually present in all smears.

(4) *Diphtheroid bacillus xerosis type*.—This is a small Gram-positive, non-motile bacillus about 2 μ in length with rounded ends. They lie side by side in palisade form, seldom end to end, and never in chains. It grows on plain agar, and produces no change in litmus milk. On Hiss's dextrose-gelatin agar it grows along the line of the stab, but produces no gas or turbidity. It is non-pathogenic to guinea-pigs.

(5) *Factor-producing bacillus*.—He found this organism on several occasions. It is 1·5 μ long by 0·5 μ broad. Grows on all media in large greyish colonies and covers the entire surface. It is non-motile, produces gas in Hiss's dextrose-gelatin agar, and liquefies beef serum.

(6) *Staphylococci*.—Always present.

Gurd states that organisms (2), (3), (4), and (5) are frequently found. More rarely he encountered bacilli belonging to the proteus group, and also several types of chromogenic cocci.

Ohlmacher (1908) found a xerosis type of diphtheroid associated with the gonococcus in several acute cases of gonorrhœa. He also obtained a similar diphtheroid in the lungs of epileptics, and in the heart blood in cases dying in the status epilepticus; also in pneumonic lungs and in two cases of chronic unhealed empyema, and in a case of abscess in the cheek. In a case of typhoid fever with meningitis he found them in the brain. He

states that the germ is non-pathogenic to guinea-pigs, producing neither local nor general reactions.

Saxe (1909) found mixed infections in 86 per cent of 108 old prostatic gonorrhœal affections. The gonococcus occurred without other organisms in only 5 cases, and all of these were of less than one year's duration. The older the case the more prevalent was the mixed infection. Staphylococci occurred in 74 per cent, bacilli in 28 per cent, Gram-positive diplococci in 10 per cent, and streptococci in 7.6 per cent of the cases with mixed infection.

Eyre and Stewart (1909) state that *B. xerosis*, embracing several varieties of diphtheroid bacilli, is rarely absent from the diseased genital tract. It grows in the form of moist translucent raised colonies indistinguishable from the gonococcus.

Jadassohn (1910) states that in gonorrhœa the urethral glands may become infected with staphylococci, streptococci, and *B. coli*. When the openings of the ducts are closed, the gonococci may die out but the other germs may lead to abscess formation. The occurrence of gonococci with secondary organisms, however, has been noted in peri-urethral, prostatic, and Bartholin abscesses, also in cystitis, pyonephrosis, and in pyosalpinx. Nevertheless, secondary infections in which no gonococci can be detected are reported to be more common. Thus we may have peri-urethral, prostatic, and Bartholin abscesses, also lymphadenitis, cystitis, pyelitis, peri- and para-metritis, and pyosalpinx, with absence of gonococci.

The Bartholin glands are especially liable to become infected with anaerobes such as *B. funduliformis*, *B. fœtidus*, *B. caducus*, and the *Crinco-coccus* "*Halle*." *B. pyocyaneus* may be found, but only very seldom. Occasionally there occur *B. perfringens*, *B. xerosis*, and very rarely tubercle bacilli.

Linder (1910) describes the bacteriology of urethritis in which no gonococci can be found.

v. Wahl (1911) believes that the so-called chronic gonorrhœa is not caused by the gonococcus, but is due to a diplococcus very similar in appearance, but not so definitely Gram-negative, which occurs in smaller groups. It is found mostly free in the secretion. In cultures it shows greyish-white colonies which do not show the porcelain-like appearance so characteristic of gonococci. It grows easily on plain agar, and forms delicate chains. He considers that this diplococcus is the cause of vulvo-vaginitis in little children and the chronic urethritis in adults after acute gonorrhœa. These observations, however, have received no confirmation from other workers. Recently, however, Broughton-Alcock has isolated a small diplococcus from very chronic cases of gonorrhœa. These resemble the gonococcus in their cultural characteristics, but they tend to be Gram-positive. Unlike v. Wahl's diplococcus, however, they do not grow on ordinary agar. Indeed, Broughton-Alcock's organism would only grow very delicately on the very best gonococcal medium, such as human plasma agar. The author has confirmed these observations.

Kreissl (1912) gives an account of chronic gonorrhœa and mixed infection. The author has been unable to gain access to his work.

Shaw (1917) states that cultures from the female uro-genital tract in cases of chronic gonorrhœa invariably yield staphylococcus albus and pseudo-diphtheroid bacilli, with or without the presence of gonococci. He mentions two species of the pseudo-diphtheria bacillus.

(1) *A Hoffmann type*.—Gram-positive, and probably identical with the xerosis bacillus found in conjunctivitis. The colonies are nearly white, and larger than those of the true diphtheria bacillus. It forms no acid in glucose-litmus broth, and is non-pathogenic to guinea-pigs.

(2) *True diphtheroid type*.—He states that this variety is the more common of the two. It is larger, variable in size, and more like the true diphtheria bacillus morphologically. It grows slowly, forming opaque white colonies on agar, resembling those of streptococci. When examined with a lens they show a crenated margin and a crinkled surface.

Both types are found in the urethra of both sexes, also in the uterus and in cases of

pyosalpinx. He considers that these bacilli along with the staphylococcus albus are responsible for keeping up the persistence and chronicity of the discharge in old cases of gonorrhœa in both sexes. He found similar bacilli in skin sinuses, also in the nose and mouth. This author frequently obtained *Saccharomyces albicans* from the vagina by culture, and also certain species of streptococci in long or short chains, with the individual cocci slightly elongated in shape. The size of the cocci varied considerably in the cultures. He seems to have been at a loss as to the exact nature and identity of these streptococci, and points out that the varieties of such organisms are somewhat complex. He gives the following list of streptococci obtained from various sources :—

- (1) *Streptococcus tenuis* (Veillon).—Very small oval cocci 2-6 in a chain.
- (2) *Streptococcus brevis* (v. Lingelsheim).—Chains of 4-6 diplococci.
- (3) *Streptococcus longus* (v. Lingelsheim).—Forming very long chains.
- (4) *Streptococcus equinus* (Andrewes and Horder).—Saprophytic from the herbivorous intestine.
- (5) *Streptococcus mitis* (Andrewes and Horder).—Saprophytic.
- (6) *Streptococcus pyogenes* (Andrewes and Horder).—Pathogenic, found in pus and in erysipelas.
- (7) *Streptococcus salivarius* (Andrewes and Horder).—Short chains from saliva and intestines.
- (8) *Streptococcus anginosus* (Andrewes and Horder).—Long chains from mouth in scarlet fever, also from the intestine.
- (9) *Streptococcus faecalis* (Andrewes and Horder).—Short chains from the intestine.
- (10) *Pneumococci* (Andrewes and Horder).—Characterised by having a capsule.

Andrewes and Horder classified these streptococci according to their sugar fermentation reactions.

Thomas, Ivy, and Birdsall (1914) found that polyvalent antigens made from meningococci, pneumococci, streptococci, *B. coli*, or corny bacteria occasionally gave positive reactions in cases of gonorrhœa. They explain this as being due to the supervention of mixed infections in the urethra.

Madden (1915) states that mixed infections occur very frequently in gonorrhœa. The commonest organisms are staphylococci, a short bacillus, a diphtheroid bacillus, and diplococci of various sizes. He gives the following list of germs found by Professor Ferguson (University, Cairo) :—

Staphylococci of all kinds ; short coli-like bacilli ; cocci resembling pneumococci ; less definite diplococci larger than gonococci and Gram-positive ; diphtheroid bacilli ; and short, stout bacilli.

Culver (1916) investigated the bacteriology of chronic prostatitis and spermato-cystitis. His paper records the results of an examination of 34 patients, of whom 26 suffered from subacute or chronic arthritis, and a principal object of the investigation was to demonstrate the connection between arthritis and prostatitis. An account of previous work by other observers is given, and the author's technique is described. Organisms were found in 24 cases (70 per cent), but the remaining 10 were not examined more than three times, and repeated examination is often required before organisms are obtained. Anaerobic as well as aerobic germs were found in one-sixth of the series. In 66 per cent of the cases tested the organisms isolated seemed to be specific, on the evidence of positive immunological reactions following the injection of the autogenous organisms, and specific focal reactions pointed strongly to the conclusion that the chronic infections of the prostate and vesicles were responsible for the arthritic symptoms. The writer found good results follow the drainage of the focus of infection and vaccination with the isolated organisms. Twelve different organisms were isolated from 24 cases ; no relationship was noted between any one organism and any particular group of symptoms. The organisms most frequently found were staphylococcus albus, streptococcus hæmolyticus, the gonococcus, and a diphtheroid bacillus.

The Secondary Organisms found by various Observers in Gonorrhœal Complications and Metastatic Affections. The pseudo-gonococci found in such conditions have already been mentioned in Chap. XIII.

Zweifel (1884), Krönig (1893), and Finger (1905) believe that the genital complications in gonorrhœa, such as epididymitis, salpingitis, etc., are originated by the gonococcus alone, but that the metastatic complications like glandular involvement (bubos), arthritis, cardiac lesions, and skin abscesses are usually caused by mixed infections.

Nasse and Rindfleisch (1897) on the contrary state that the gonococcus itself is the chief cause of arthritic complications, and that mixed and secondary organisms are of limited importance in this affection.

Baur (1901) states that gonococci can usually be cultivated from joint complications in the early stages not later than the sixth day, and that mixed or secondary organisms are seldom found. In some exceptional cases he found staphylococci along with the gonococcus, and very rarely he obtained streptococci or staphylococci alone.

Scholtz (1903) found the gonococcus in the skin in a case of hyperkeratosis with skin abscesses.

Buschke (1899) on the contrary believes that these hyperkeratotic conditions of the skin are due to the circulating toxins of the gonococcus, but that the germ itself does not inhabit the lesions.

Cassel (1903) records a case of an abscess in the back of a child following gonorrhœal ophthalmia. He obtained a pure culture of gonococci from this abscess.

Andrewes (1904) gave a list of 684 cases of pyosalpinx diagnosed chiefly from microscopic film preparations. Of these 5 per cent showed sterile pus, 22.5 per cent showed gonococci only, 6 per cent showed only saprophytic organisms. The remainder presented a variety of pyogenic organisms.

Wynn (1905) considers that secondary organisms play a rôle in complicated cases, and that they complete the work begun by the gonococcus. He thinks that *B. coli* is one of the most frequent complicating organisms. This germ is very commonly found in cystitis and other diseases of the urinary passages. He describes three cases of gonococcal pyæmia. One case showed subcutaneous abscesses, from which he obtained *B. coli* as well as gonococci. The other cases presented abscesses in the lungs, kidneys, hip, etc., from which he obtained *B. coli* and staphylococci in addition to the gonococcus.

Jadassohn (1910) states that gonococci, together with other organisms, have been found in such complications as arthritis, endocarditis, muscle abscesses, and in multiple pyæmic affections; but that more frequently only secondary germs without gonococci are reported to occur in such complications, for example in peritonitis, epididymitis, arthritis, endocarditis, pleurisy, skin lesions, eye diseases, meningitis, and spinal abscesses.

Menge (1910) believes that mixed infections in the female are of little importance, and that true mixed infections seldom occur. He maintains that complications due to direct extension of the disease and also metastatic infections are caused by the gonococcus alone. He admits, however, that secondary organisms do occur in metastatic complications.

Norris (1913) is of the opinion that mixed, or rather secondary, infections are by no means infrequent, more especially in chronic cases.

Shaw (1917) has found diphtheroid bacilli in pyosalpinx and in suppurating ovarian cysts.

Nicoll (1912-13) reports on a case of general gonococcus infection in a child in which gonococci and Gram-negative bacilli were obtained by culture from the urethral discharge. A culture from the shoulder-joint presented gonococci, and one from an abscess of the sterno-clavicular joint showed a mixed growth of gonococci and Gram-negative bacilli.

Hastings (1913) investigated 24 cases of arthritis by means of the complement-fixation test, using antigens of streptococci, staphylococci, and gonococci obtained from the prostatic secretions. Four positive reactions were obtained with the gonococcal antigen, and three positives with the streptococcal antigen. Twelve cases were negative to both.

One case which had had gonorrhœa fifteen years previously, was given gonococcal vaccine without any beneficial effect. Cultures made from the expressed prostatic secretion developed on two occasions a typical *Streptococcus mitior*, and an autogenous vaccine of this organism was injected. It produced a focal reaction in the joints, and caused a marked improvement in the condition. In a second almost identical case the autogenous streptococcal vaccine brought about a rapid improvement of the joints. From a third case he cultivated streptococci twice from the prostatic secretion, but had no opportunity of testing the effect of a vaccine. He concludes that some cases of arthritis deformans are infective in nature, and that the infecting germ may be a *Streptococcus viridans* or a gonococcus. His experiments seem to indicate that secondary organisms play some rôle in cases of gonorrhœal arthritis.

The author on one occasion treated a case of supposed gonococcal rheumatism with gonococcal vaccine, with little or no benefit. Cultures were then prepared from the prostatic secretion, and a pure culture of a Gram-positive diplococcus, resembling the pneumococcus or an enterococcus, was obtained. Subsequent treatment with a vaccine prepared from this organism produced a rapid recovery.

According to Besson (1914) numerous secondary organisms found in gonorrhœa are described by Bumm, Eraud and Huguoneng, Steinschneider, Legrain, Eisenberg, Bosc, etc., and can cause diverse complications, such as abscesses, suppurations, endocarditis, etc.

Madden (1915) states that much better results are obtained by mixed vaccines of gonococci and secondary organisms in local complications such as cystitis, urethritis, pyelitis, prostatitis, and epididymitis, than with pure gonococcal vaccine. This would also appear to support the view that mixed infections play a part in the complications of gonorrhœa.

Bowers (1915) states that while it is true that the gonococcus is the primary cause of the majority of pelvic complications, nevertheless it must be borne in mind that it is a single infection for a very short time, not more than two or three days, and that the nature of the mixed infection is of much importance. When the complicating organism is the staphylococcus or the colon bacillus, the outlook is usually favourable; but when it is a streptococcus or pneumococcus, a very guarded prognosis is necessary.

Buschke and Hirschfeld (1915) describe a case of staphylococcal septicæmia with aplastic anæmia following gonorrhœa. The man developed multiple arthritis soon after acquiring gonorrhœa, and then staphylococcal sepsis developed, which was fatal in three months. The necropsy revealed acute nephritis. There was an abscess of the lung. The marrow of the long bones was yellow and contained staphylococci. The blood showed severe aplastic anæmia.

Rosenow and Davis (1916) proved experimentally that streptococci, derived from inflammatory conditions of the human ovaries, showed an elective affinity for the ovaries of animals. Cultures from ovaries removed at operations yielded *Streptococcus viridans* in a large number of cases. The gonococcus, the Welch bacillus, *Staphylococcus albus*, the colon bacillus, and diphtheroid-like bacilli were also obtained. Microscopic preparations of the ovaries showed the presence of diplococci in several instances. Cultures of streptococci isolated were injected into rabbits and dogs and were recovered from the ovaries of these animals.

It seems rather significant that Hastings should also refer to a *Streptococcus viridans* as occurring in the prostate and in the joints. The reader will no doubt obtain from these accounts the feeling that a man with a chronic gleet full of secondary organisms cannot be considered as entirely safe to marry even although no gonococci are present.

Organisms found in Venereal Warts. Civatte and Favre (1919) made sections of venereal warts. These were fixed in formalised bichromate solution and stained with hæmatoxylin. They were able to differentiate three types of spirochaetes:—(1) A straight form measuring 10-15 μ , with blunt ends. These were frequently nearly straight, but sometimes showed some curving or resembled a comma or mark of interrogation. (2) A

distinct spirillar type, with tapering ends and a length about four times the diameter of a red cell. These possessed from ten to twelve fine spirals. (3) A form with tapering ends, shorter and thicker than the preceding, but longer than the first type. Type (3) showed four or five regularly placed coils which were bolder and more regular than the more frequent spirals of the second type.

The type (3) spirochætes were never very frequent in a section, and were never seen in the interior of the cells. The first two types were always associated, and formed intracellular and extracellular spirochætal tufts which are characteristic of venereal warts. Of these two associated types the first is especially abundant in the early stages of venereal warts. On comparing sections stained with iron-hæmatoxylin with others prepared by the silver impregnation method, the straighter type of organism does not take the silver so well, whereas the spirillar forms show up well with the silver method.

These spirochætes do not correspond either with *Treponema refringens* or with *T. pallidum*; the latter more particularly does not stain by the hæmatoxylin method. The writers have found spirillar forms in sections stained by their method in cases of pemphigus vegetans, papillomatous lymphioma of the tongue, ulcerative stomatitis, cancer of the penis, and syphilitic condylomata of the anus and vulva; but in all these cases the type of spirochæte found differs in one respect or another from the types found in venereal warts. The characteristics of the last are the constant association of the two types, their enormous numbers in the lesions, and their intracellular distribution.

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CHAPTER XV

SECONDARY ORGANISMS—AUTHOR'S RESEARCHES

IN early acute gonorrhœa, if the meatus is carefully wiped with sterile gauze, saturated with spirit, and a loopful of the expressed pus inoculated on to a slope tube of the author's medium, a growth of the gonococcus is nearly always obtained. The culture in many cases is free from other organisms. Where, however, the patient has been irrigated, and in practically all chronic cases, growths of secondary organisms are obtained. In old gleet cases slope cultures made from the discharge seldom show the gonococcus, but give, as a rule, a profuse growth of staphylococci, diphtheroids, pneumococci, *B. coli*, etc. A pure culture of one of the latter may be obtained, but more frequently there is a mixed growth of two species such as staphylococci and diphtheroids. A mixture of three types is quite common, and more rarely even four different varieties occur.

If the gonococci are not found in smear preparations by the microscope, it is very unlikely that they will be obtained by making a slope culture. Culture diagnosis by this method can hardly be considered superior to the microscopic diagnosis. The reason for this is that when the gonococci are very scarce, the growth is not likely to become distinctly visible for three, four, or even five days, by which time, as a rule, the secondary organisms in slope tubes have overgrown and obscured them. When the culture diagnosis, however, is carried out properly by carefully spreading a drop of the discharge over a plate of good medium, the chance of finding the gonococcus is certainly greater than in the case of microscopic examination of a smear. It is most important in such cases not to discard the plate until it has incubated for at least five days. The author has seen minute colonies of gonococci appear after seven days' incubation on a good brand of glucose-plasma agar, and when these minute colonies were spread out over the surface with a platinum loop a profuse sheet of growth developed next day. The delay in the initial appearance of the colonies was due, no doubt, to the fact that they had each developed from a single isolated gonococcus, which was probably in a devitalised state at the time of incubation.¹

For the isolation of the gonococcus on plates the author has used glucose-plasma agar faintly tinted with crystal violet. The latter inhibits the growth of staphylococci, but the gonococcus is not affected even although the colonies take up the stain. This is also an excellent method of isolating the gonococcus from a contamination with *B. subtilis*. The subtilis bacillus is apparently markedly inhibited by the crystal violet. Pneumococci and coliform organisms, on the other hand, do not seem to be affected by it. There can be no doubt that by the use of such a method gonococci could be isolated from a considerable number of old chronic gleet cases, and in the case of vaginal discharges

¹ The plates must be placed in a closed glass vessel containing a piece of moist gauze, otherwise the medium will dry up before the five days have elapsed.

one might even obtain a higher figure than the 60 per cent of positive findings recorded by Gurd.

The author is inclined to believe, however, that for diagnosis in all such obscure cases the complement-fixation test is much more delicate and not quite so tedious.

The author employs microscopic examination and complement-fixation for diagnosis. Cultivation is used chiefly for the isolation of the gonococcus and the various secondary organisms in order to obtain autogenous vaccines. To obtain cultures of the secondary infecting germs in chronic cases, the meatus is cleansed with alcohol and the urine passed into a sterile flask or bottle. Ten cubic centimetres of this are transferred to a sterile tube and centrifuged at a high speed for about ten minutes. The deposit obtained is inoculated by means of a sterile pipette on to a slope-culture tube. From 230 urine cultures prepared in this manner the following organisms were obtained:—

Organisms found in the Urine Deposits (Males) in Chronic Gonorrhœa

Staphylococcus albus in 69 per cent.

This organism varied in size. Very large types occurred in 23 per cent of the cases. Sometimes large and small types occurred together.

Species of pneumococcus or enterococcus in 23 per cent.

Diphtheroids (Hoffmann type) in 22 per cent.

Coliform organisms in 14 per cent.

Species of strepto-pneumococcus in 10 per cent.

True diphtheroids (clubbing) in 8 per cent.

Gonococci in 8 per cent.

Gram-negative diplobacilli in 2.6 per cent.

True streptococci in 1.8 per cent.

Gram-negative sporing bacilli in 1.7 per cent.

Gram-negative diplococci (not gonococci) in 1.7 per cent.

Long diphtheroids, with remarkable involution form in 1 per cent.

Large Gram-positive sarcina once out of 230 cases.

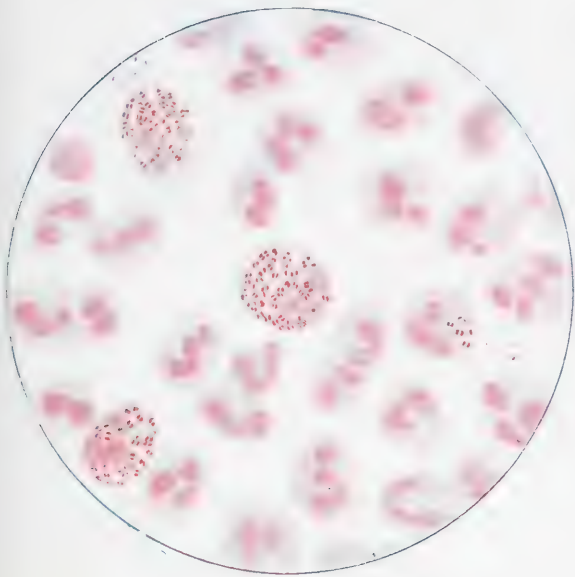
A yeast (pink colonies) once out of 230 cases.

A large Gram-positive bacillus once out of 230 cases.

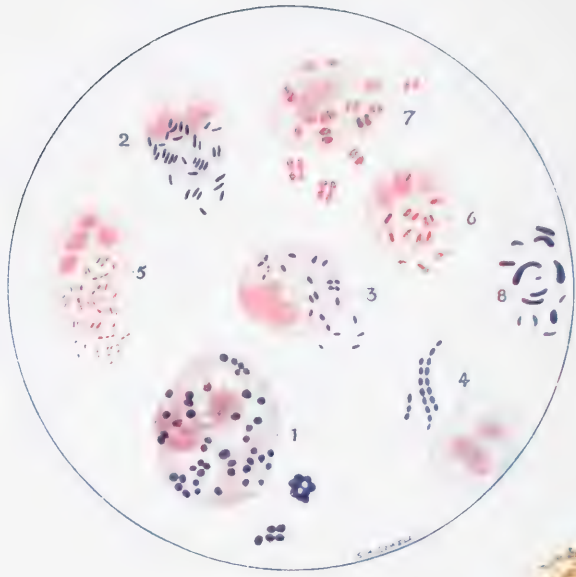
A Gram-negative streptothrix once out of 230 cases.

The cultures in the above cases were not, as a rule, incubated for more than twenty-four to forty-eight hours. Had these urine deposits been plated and allowed to incubate for five to seven days, a much larger variety of organisms would no doubt have been obtained, such as *staphylococcus citreus*, *flavus*, etc. Nevertheless, the list probably represents fairly accurately the most common secondary germs which occur in chronic gonorrhœa and the frequency with which they are found. Most observers seem to have found a streptococcus in a considerable number of cases. The author is inclined to think that many of these may not have been the true streptococcus, but a species of strepto-pneumococcus or enterococcus, wherein the individual cocci in the chains show a definite lanceolate shape.

With regard to the Gram-negative diplococci (not gonococci), *M. catarrhalis* and the meningococcus were never found. All were larger than the gonococcus, so that there was little difficulty in distinguishing them. The growth also was entirely different. One type resembled the gonococcus very closely in size, but some forms were more elongated, resembling a very short stout diplobacillus. The growth, moreover, was very profuse. It was soluble in alkali, but an antigen prepared from it did not give a positive reaction with gonorrhœal sera.



A



B

PLATE I.

Drawings from gonorrhoeal urethral smears, stained by Gram's method (Jensen's modification). Magnification, about 1,000 diameters.

- A.—Shows pus cells containing intracellular gonococci, also some lying extracellularly. Note that they are Gram-negative and kidney-shaped.
- B.—This is a composite drawing made up from various urethral smears to show the different varieties of secondary organisms which frequently occur in gonorrhoeal pus, more especially in chronic cases. All these secondary organisms may occur within pus and epithelial cells, but more commonly they lie extracellularly. Nos. 1 to 6 are painted from the actual specimens. Nos. 7 and 8 are somewhat diagrammatic. Nos. 1, 2, 3 and 5 are the most common types found.
- 1.—Pus cell showing *Staphylococcus albus*—Gram-positive. Note that some are lying partially digested in vacuoles and have lost their Gram-positive character.
- 2.—Pus cell showing a diphtheroid bacillus (Hofmann type)—Gram-positive.
- 3.—Pus cell showing a short Gram-positive *Diplobacillus* with pointed ends, indistinguishable morphologically from the *Pneumococcus*.
- 4.—Shows a similar organism to No. 3, except that it occurs in chains, resembling a *Streptopneumococcus*.
- 5.—Shows a small *Diplobacillus*—Gram-negative. It assumes various shapes and coccoid forms; the latter are not kidney-shaped but lanceolate.
- 6.—Pus cell with a large Gram-negative bacillus.
- 7.—Shows the *Diplococcus magnus* of Rosenthal (?) or "*Pseudogonococcus*." It is weakly Gram-negative, and is four times as large as the *Gonococcus*. It occurs rarely in the urethra, more commonly in cases of conjunctivitis.
- 8.—Shows a diphtheroid bacillus with clubbing and involution forms—Gram-positive.

Organisms found in the Vaginal Discharge of Twenty-five Cases of Gonorrhœa

The discharge was examined by smear and by slope culture, and the following germs were found :—

Staphylococcus albus in 70 per cent.
 Diphtheroids (Hoffmann type) in 52 per cent.
 Döderlein's vaginal bacillus in 48 per cent.
 Species of pneumococcus in 44 per cent.
 Gram-negative diplobacillus in 36 per cent.
 Gonococcus in 28 per cent.
 Coliform bacilli in 20 per cent.
 Strepto-pneumococci in 16 per cent.
 Diphtheroids (clubbing species) in 4 per cent.
 Yeasts in 4 per cent.

The flora, therefore, is very similar to that in the male, except for vaginal bacilli and the much more common occurrence of Gram-negative diplobacilli and yeasts.

Organisms found in Gonorrhœal Complications

(a) **Gonorrhœal Joints.**—Four cases. The fluid proved to be sterile in three cases. From the fourth case (a suppurating ankle-joint) both *Staphylococcus albus* and the gonococcus were cultivated.

(b) **Epididymitis.**—Seven cases. By puncture and inoculation of cultures the gonococcus was obtained pure in two cases. In other three a diphtheroid (Hoffmann type), a diphtheroid (clubbing type), and a diphtheroid (with remarkable involution forms) were found respectively. From the remaining two cases *B. coli* was isolated by culture.

(c) **Cystitis.**—Two cases. *Staphylococcus albus* and *B. coli* were grown from one, and a large type of *Staphylococcus albus* from the other.

(d) **Pus from Cowper's Gland.**—One case. From this a pure growth of the gonococcus was obtained.

(e) **Pus from Tyson's Gland.**—One case. The culture showed a pure growth of a Hoffmann diphtheroid.

(f) **Bubo in Groin.**—Three cases. From two *Staphylococcus albus* was cultivated, and from the third a large type of Hoffmann diphtheroid.

(g) **Gonorrhœal Warts.**—One case. Culture showed staphylococci, pneumococci, and the diphtheroid with remarkable involution forms.

(h) **Gonorrhœal Sores on Exterior of the Penis.**—One case. Culture showed gonococci, *Staphylococcus albus*, and a Hoffmann diphtheroid.

(i) **Ophthalmia.**—Three cases. From the first the following organisms were obtained : gonococcus, *Diplococcus magnus* of Rosenthal (Gram-negative), sarcinæ (Gram-negative), diphtheroids of Hoffmann type, and *Staphylococcus albus*. From the second, staphylococci and Hoffmann diphtheroids were grown; and from the third, which was probably not gonorrhœal, only *Staphylococcus albus* was obtained.

(j) **Hyperkeratosis.**—Six cases. In all the hard skin was carefully removed as aseptically as possible, and the cheese-like material below was inoculated on to plasma agar slope tubes or plates. From three no growth of any organism was obtained.

From the fourth very delicate colonies of a Gram-positive cocco-bacillus were obtained. In the fifth case, the first culture grew *Staphylococcus albus* and pneumococci. With a second attempt, however, the culture tube remained sterile.

In none of the above five cases could any gonococci be detected in smear preparations made from the cheesy material.

The sixth case, which was a very severe one, was investigated very carefully. Gonococci and the peculiar diphtheroid with remarkable involution forms were obtained from the urethra. The skin was obviously infected with a whole host of secondary organisms, and cultures gave a profuse growth of *Staphylococcus albus*, diphtheroids, and Gram-negative bacilli. In some of these cultures a few Gram-negative diplococci were obtained, but all attempts to isolate the latter in pure culture failed, so the presence of gonococci remained uncertain. Smears from the contents of recent blebs showed Gram-negative diplococci resembling gonococci, also staphylococci and diphtheroids which tended to club.

Details of the various Secondary Organisms found in Gonorrhœa

(a) **Staphylococcus albus.**—This undoubtedly is the most common secondary infecting organism. It occurs in about 70 per cent of all chronic cases. There are several types, which may be divided into three groups according to their size, viz. a small type, a moderate-sized type, and a very large type. Sometimes the small and large types may occur together. In smear preparations staphylococci are probably found most frequently extracellular, or lying over the surface of the epithelial cells. It is quite common, however, to find them ingested in large numbers by the leucocytes. This germ is markedly Gram-positive, but partially digested or disintegrated forms lying within the pus cells become Gram-negative. One must be careful not to mistake such for intracellular gonococci. On the other hand, gonococci and staphylococci may be found lying together within the same leucocyte, even in early acute cases. It is commonly found mixed with diphtheroid bacilli in chronic gleet (see coloured Plate II., Figs. 2 and 3; also Plate V., Nos. 1-6).

(b) **Several Types of Diphtheroid Bacilli.**—These bacilli, comprising about five different species, occurred in about 31 per cent of chronic gleet (see Plates VI. and VII.).

(1) The commonest species was a Hoffmann-like form (Gram-positive) occurring in 22 per cent of cases. It was found lying extracellularly, but frequently occurred also within the pus cells and the epithelial cells. Epithelial cells containing large numbers of this organism usually showed multitudes of Gram-positive granules. This germ grew profusely on plasma-glucose agar, and did not cloud the medium within twenty-four hours. The growth, as a rule, was whitish, with a faint tinge of greyish yellow. It also grew well on ordinary glucose agar, but showed little or no growth on gelatin at 22° C. The cultures were odourless.

The sugar reactions were as follows :—

Litmus.	Milk.	Cane Sugar.	Dulcité.	Mannite.	Lactose.	Maltose.	Glucose.	Lævulose.
No effect	Slight acid ?	Nil	Nil	Nil	Nil	Nil	Nil	Slight acid ?

No gas was produced in any of the tubes.

Microscopically this bacillus, as a rule, showed pointed ends, and two darkly stained granules were noted within its substance. The germs, as a rule, lay side by side in palisade formation, practically never end to end. Chinese letters and Y-shaped groups were common. No definite involution forms or clubbing were observed in old cultures.

It did not appear to be pathogenic, since a guinea-pig, 250 grams weight, survived a dose of fifty thousand millions injected intra-peritoneally.

(2) The next most common variety was a true diphtheroid (Gram-positive), which showed marked clubbing in old cultures. It occurred in 8 per cent of chronic gleet, often in very persistent cases. It was found lying both within the pus cells and extracellularly.

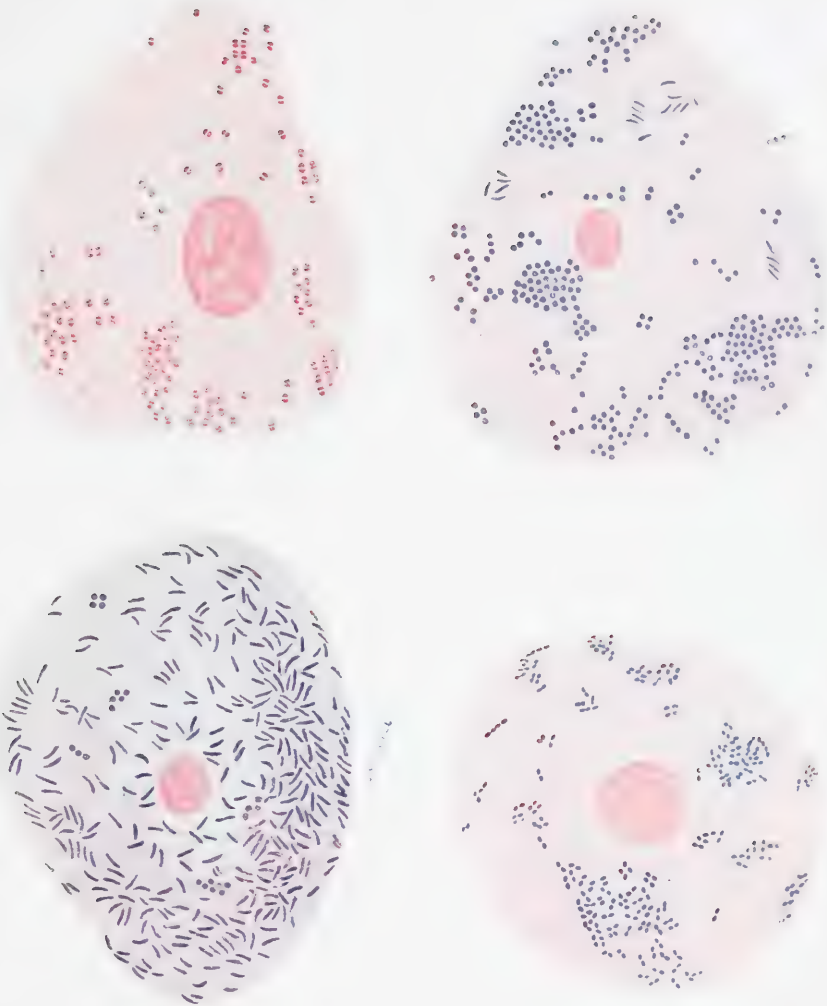


PLATE II.

Drawings from gonorrhoeal urethral smears, stained by Gram's method (Jensen's modification). Magnification, about 1,000 diameters.

- 1.—Shows an epithelial cell containing numerous *Gonococci*.
- 2.—Shows an epithelial cell containing many *Staphylococci* and a few diphtheroid bacilli (Hofmann type).
- 3.—Shows an epithelial cell containing diphtheroid bacilli (Hofmann type) and a few *Staphylococci*.
- 4.—Shows an epithelial cell containing numerous Gram-positive *Diplobacilli* resembling *Pneumococci*.

There appeared to be two or three different species. On glucose-plasma agar it produced a characteristic granular growth, consisting of small whitish colonies, difficult to emulsify. The growth was comparatively slow, and clouding of the medium was never produced. No odour was noticeable. It also grew on ordinary glucose agar, but only very slowly and feebly. No growth took place on gelatin at 22° C. It did not produce any acid or gas in litmus milk, cane sugar, dulcitol, mannitol, lactose, maltose, glucose, or levulose. Microscopically a twenty-four hours' culture showed small bacilli lying in Chinese-letter patterns. No granules were noticeable. In cultures of three or more days old large curved and clubbed involution forms appeared, as shown in the microphotograph No. 4, Pl. VII.

It did not show any particular pathogenicity, since a guinea-pig (310 grammes weight) survived an intra-peritoneal injection of twenty thousand millions without any noticeable effect.

(3) A diphtheroid with very remarkable involution forms occurred in 1 per cent of the cases. It was also found in a gonorrhoeal wart. It was an extremely delicate grower, forming only minute whitish points even on glucose-plasma agar. It did not appear to grow on ordinary glucose agar. The involution forms appeared very early in the cultures, within twenty-four to forty-eight hours. They varied in size from minute dots to long, straggling, twisted forms showing remarkable nodes and swellings. The organism was Gram-positive, but the large involution types tended to become Gram-negative. In smears the actual involution varieties were very noticeable in several cases (see Pl. XI., No. 4).

The sugar reactions and pathogenicity were not tested.

(4) A long, thin Gram-positive diphtheroid, as indicated in No. 6, Pl. VI., was only found on one occasion.

(c) **Species of *Pneumococcus* or *Enterococcus*.**—(1) A Gram-positive diplococcus indistinguishable morphologically from the pneumococcus was found in 23 per cent of the cases. This organism grew copiously on glucose-plasma agar, causing clouding and opacity in the medium. The growth was, as a rule, white and glistening and odourless. It also grew well on ordinary nutrient agar and on gelatin at 22° C. No liquefaction of the gelatin was produced. In cultures the germ showed, as a rule, complete autolysis in about three days (see Pl. VIII., Nos. 1-5).

(2) In addition to the above there occurred in about 10 per cent of cases a Gram-positive strepto-pneumococcus. The individual cocci were distinctly lanceolate in shape, like the pneumococci (see Pl. IX., Nos. 1-4).

It grew slowly in small white discrete colonies up to 1 millimetre in diameter, producing no odour. It did not cloud the glucose-plasma medium. The growth on ordinary agar was very feeble, and it tended to die out quickly. The colonies were sometimes scale-like. They were as a rule difficult to emulsify.

(d) **True *Streptococci***, in which the individual cocci were definitely round, occurred only in 1.8 per cent of the cases (see Pl. IX., No. 5).

(e) There also occurred rarely a species of **Gram-positive strepto-staphylococcus**, where the cocci were arranged partly in groups with some tendency to short chain formation. The growth on plasma agar consisted of small white colonies. An opaque milkiness was produced in the medium, but no odour.

(f) **Large Gram-negative Bacilli of the *B. coli* Type.**—These organisms occurred in 1.4 per cent of cases. They grew profusely on plasma agar, clouding the medium and producing a sour odour. The growth showed an earthy yellowish tint. They grew well on ordinary agar and on gelatin at 22° C. without liquefaction.

Microscopically long and short forms were noticeable. Some showed a terminal white unstained area at each end, and sometimes in the middle. No spores were produced. The cultures died in a few days in the incubator, but they remained alive for a long time when placed in the ice-chest. This organism was apparently motile at times. One strain tested against the various sugars gave the following fermentation reactions:—

Litmus Milk.	Glucose.	Lactose.	Mannite.	Cane Sugar.	Maltose.
Acid and Co- agulation	Acid and gas	Acid and gas	Acid and gas	Acid and gas	Acid and gas

Pathogenicity.—Guinea-pig injected intra-peritoneally died after five days.

There can be no doubt that the above group of Gram-negative bacilli comprised several species.

One species grew on the plasma agar without producing any opaque cloudiness in the medium, and the growth showed a light lemon-yellow colour. It grew feebly on gelatin at 22° C. without liquefaction. This species was a short, stout bacillus with square-cut ends. Other species—short, stout forms with more rounded ends—tended to go in pairs, and were liable to resemble and be confused with the gonococcus. Some of these latter types showed a whitish, moist, profuse growth, easily distinguished from cultures of the gonococcus (see Pl. X., Nos. 1-4).

(g) A small Gram-negative diplobacillus was cultivated from 2.6 per cent of the cases, but it occurred more frequently than this in smears. This is possibly the same germ as the Gram-negative diplobacillus found so often in chronic gonorrhœal discharges in the female, and described by Gurd as an influenzoid bacillus (see Pl. X., Nos. 5 and 6).

It grew profusely on glucose-plasma agar without clouding the medium. Its growth was transparent and slimy (not unlike the gonococcus), with a slight yellowish tinge. In artificial light it showed a distinct fluorescence. No odour was produced. It grew well also on ordinary glucose agar and on gelatin at 22° C. without liquefaction. It gave the following sugar reactions:—

Litmus Milk.	Cane Sugar.	Dulcite.	Mannite.	Lactose.	Maltose.	Glucose.	Lævulose.	Bile Salt Lactose.
Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil

Slope cultures remain alive for a long time if placed in the ice-chest.

Microscopically this organism showed a variety of shapes and sizes, from small coccoid forms to long threads. A few of the short forms showed active motility, and some appeared to have spored.

In smears of pus this germ often occurred in very large numbers, for the most part extracellular, but it also occurred within the leucocytes. The short diplo-forms were often indistinguishable from the gonococcus, but as a rule they were more lancolate in shape.

Pathogenicity.—A guinea-pig weighing 240 grammes injected with about twenty thousand millions intra-peritoneally died after eight days. The *post mortem* showed congestion of the peritoneum and omentum. The organism was not recovered from the heart blood.

(h) **Gram-negative Diplococci Pseudo-gonococci *Diplococcus magnus* of Rosenthal?**

—The type of Gram-negative diplococcus most commonly met with produced a characteristic lemon-yellow profuse growth on glucose-plasma agar, without clouding the medium. It grew well on ordinary glucose agar and also on gelatin at 22° C. with liquefaction. It remained alive in slope cultures for a long time. It did not produce any reaction with the various sugars employed.

Microscopically it was very much larger than the gonococcus, its diameter being two to three times as great. Also it was less easily decolorised by Gram's stain (see Pl. IV., Chap. XIII.).

(i) **Other Organisms rarely found.**—On one occasion the author found a streptothrix in a smear of the expressed material after prostatic massage. This streptothrix was obtained also in pure culture (see Pl. XI., Nos. 5 and 6).

In several other cases of gonorrhœa, curious thread-like organisms occurred in groups in the polymorph leucocytes. The nature of these organisms has not yet been ascertained (see Pl. XI., No. 3).

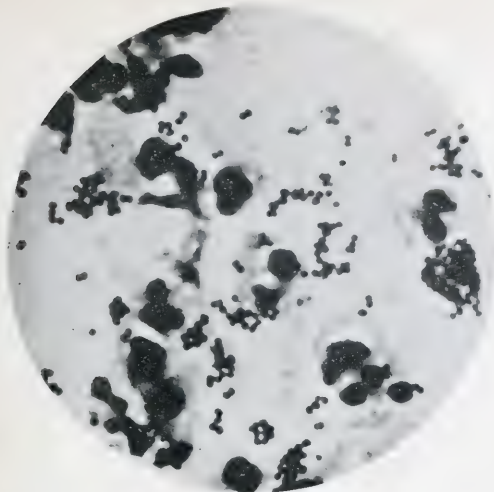
This organism is perhaps the straight form of spirochæte, described by Civatte and Favre, which occurs in tufts within the cells in gonorrhœal warts (see page 116).

EXPLANATION OF PLATE V

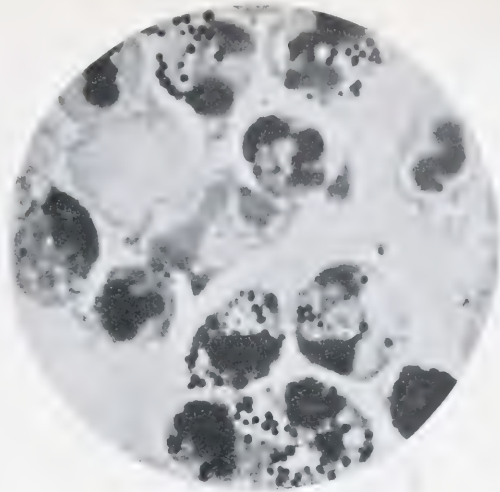
- No. 1.—Urethral smear (chronic gonorrhœa) stained Gram's method. Note the heavy infection with staphylococci, which are chiefly extracellular.
- No. 2.—Urethral smear (chronic gonorrhœa). Gram's stain. Note heavy infection with staphylococci lying within the pus cells. Some are partially digested and stain Gram-negative.
- No. 3.—Urethral smear (chronic gonorrhœa). Gram's stain. Note heavy infection with staphylococci, which are lying plastered over an epithelial cell.
- No. 4.—Smear from a culture taken from case No. 2. Note the large size of the staphylococci.
- No. 5.—Culture of staphylococcus albus from urethral discharge of a case of chronic gonorrhœa.
- No. 6.—Smear from culture tube No. 5. Note that in this case the staphylococci belong to a small type, and measure about the same diameter as gonococci.

PLATE V

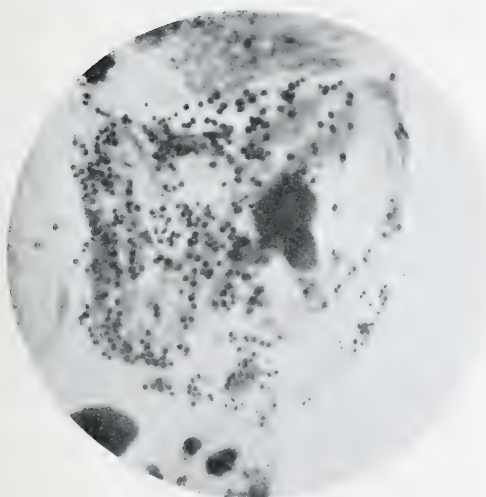
All the photographs in this plate are magnified 1000 diameters, except No. 5, which is the natural size.



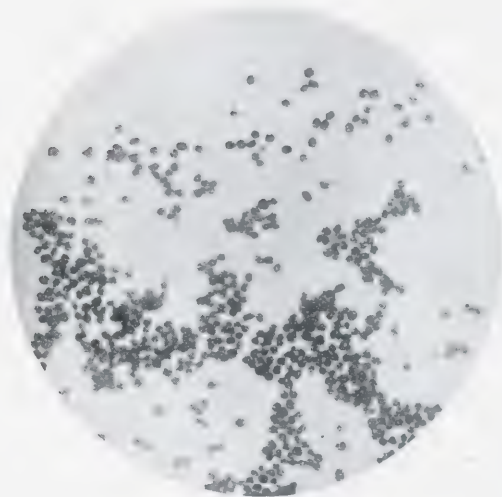
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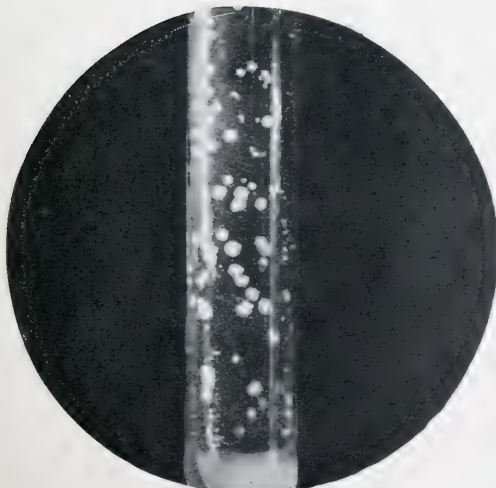
No. 2.



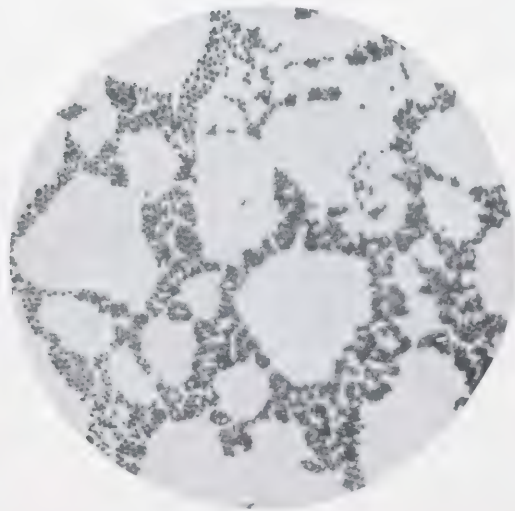
No. 3.



No. 4.



No. 5.



No. 6.

EXPLANATION OF PLATE VI

No. 1.—Urethral smear (chronic gonorrhœa) stained Gram. Note the pus cell containing diphtheroid bacilli of the Hoffmann type.

No. 2.—Smear after prostatic massage of a chronic gleet case. It shows spermatozoa, with a few staphylococci and diphtheroids.

No. 3.—Shows cultures of the Hoffmann diphtheroid obtained from the same case as No. 1.

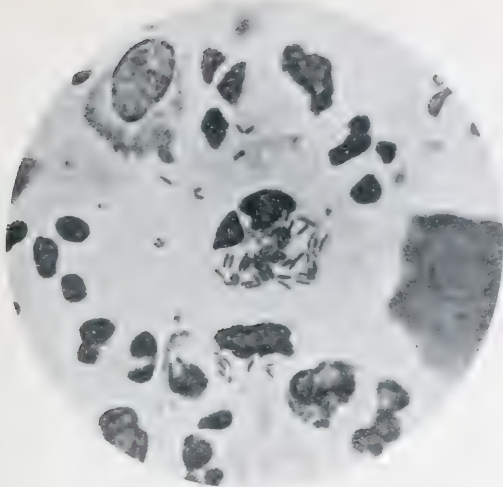
No. 4.—Shows a smear of the Hoffmann diphtheroid obtained from the culture tube No. 3.

No. 5.—Smear from another culture of a Hoffmann diphtheroid obtained from a case of chronic gonorrhœa. Note the palisade grouping of the bacilli.

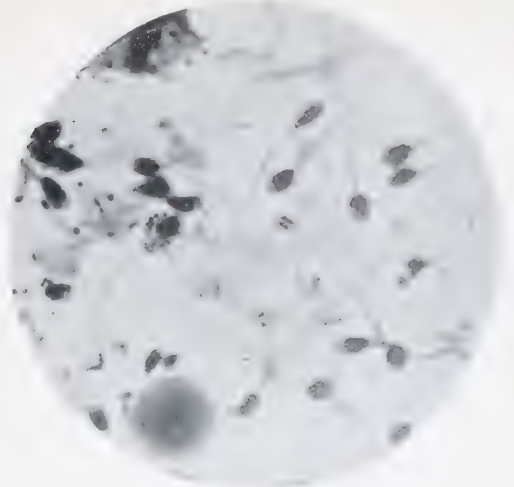
No. 6.—Smear from a culture of another species of Hoffmann diphtheroid obtained from a chronic gleet.

PLATE VI

No. 3 is natural size. Nos. 1, 2, 4, 5, and 6 magnified 1000 diameters.



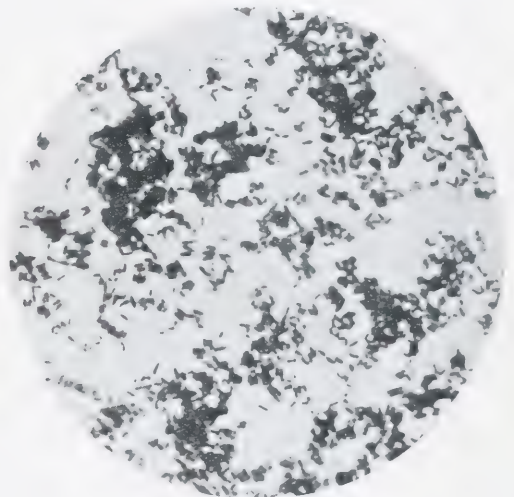
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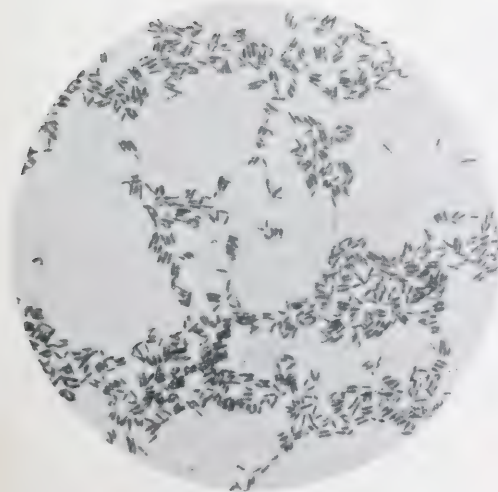
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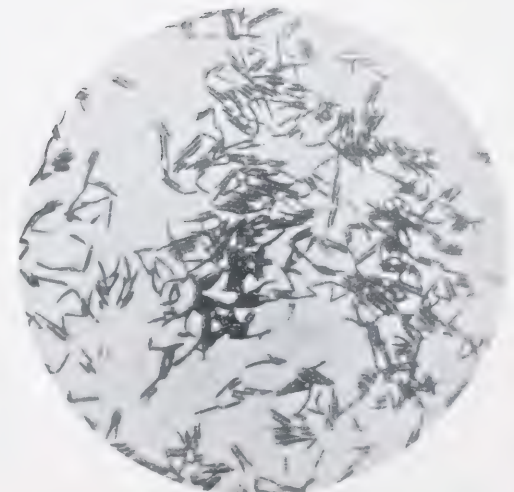
No. 3.



No. 4.



No. 5.



No. 6.

EXPLANATION OF PLATE VII

No. 1.—Urethral smear from a case of chronic gonorrhœa, showing a heavy infection with diphtheroid bacilli of the clubbing type.

No. 2.—Culture of clubbing diphtheroid obtained from the same case as No. 1. Note the granular-like growth.

No. 3.—Smear from culture tube No. 2, young twenty-four hours' culture, before any clubbing or involution forms have developed.

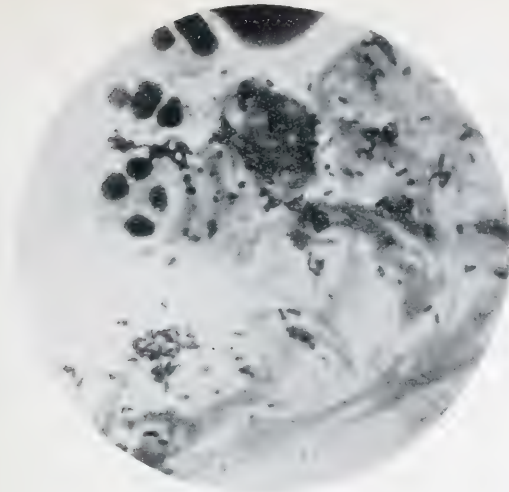
No. 4.—Smear from a culture of a similar clubbing diphtheroid, obtained from a case of epididymitis. This culture was one week old, and shows the development of marked involution forms.

No. 5.—Smear from a case of subacute gonorrhœa, showing two adjacent pus cells, one containing gonococci, the other containing diphtheroid bacilli.

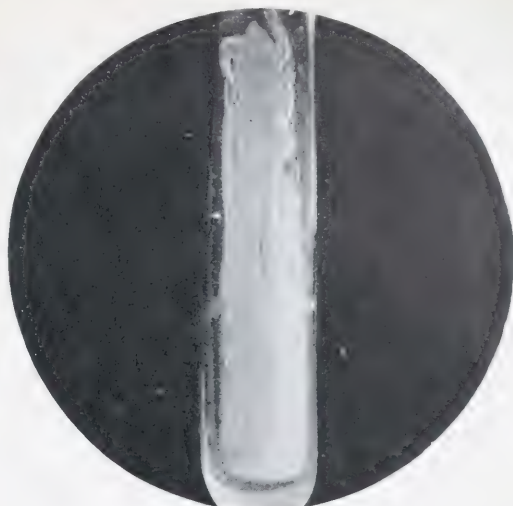
No. 6.—Vaginal smear from a case of chronic gonorrhœa with erosion of the cervix. Note the large epithelial cell, packed with diphtheroid bacilli.

PLATE VII

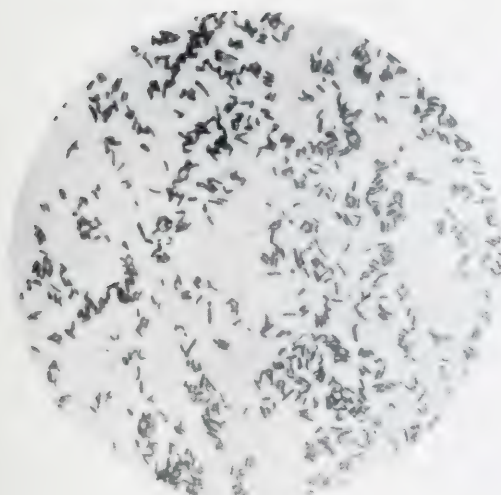
Nos. 1, 3, 4, 5, and 6 are magnified 1000 diameters. No. 2 is natural size.



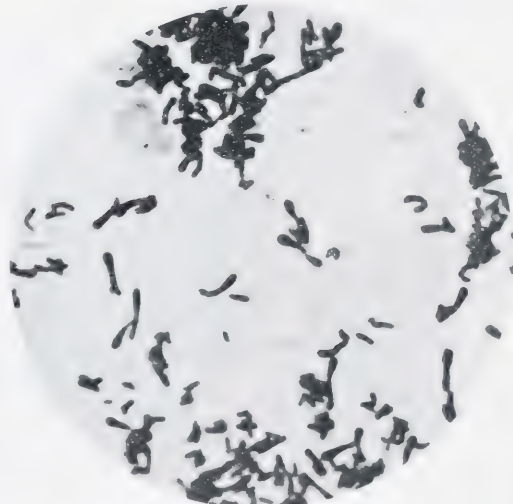
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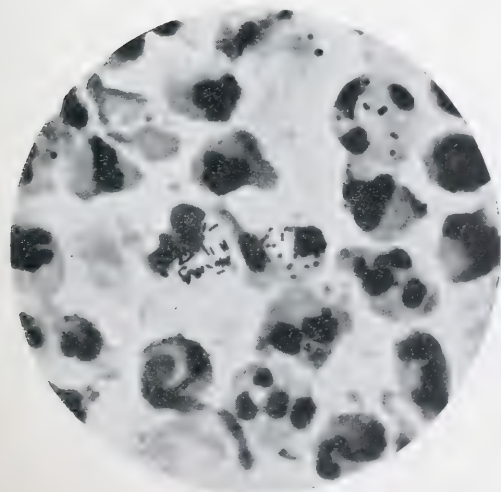
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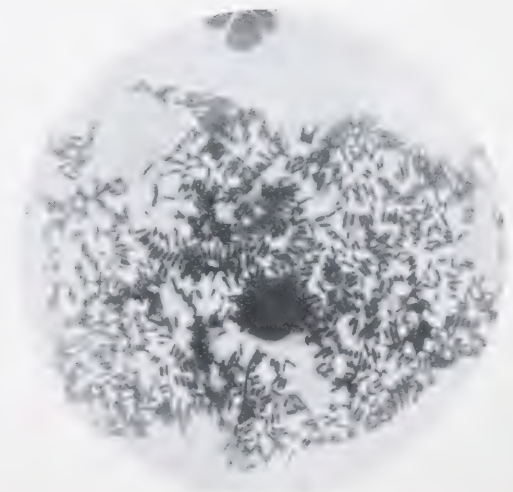
No. 3.



No. 4.



No. 5.



No. 6.

EXPLANATION OF PLATE VIII

No. 1.—Urethral smear, chronic gonorrhœa, stained Gram. Note heavy infection with pneumococcus-like organisms, which are chiefly extracellular.

No. 2.—Urethral smear from another case of chronic gleet. Note the pneumococcus-like organisms lying within the pus cells.

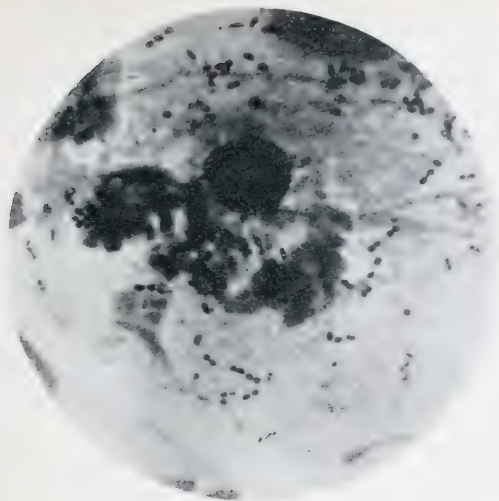
No. 3.—Smear from a culture obtained from the same case as No. 1. Note that the diplococci are lanceolate in shape and closely resemble the morphology of the pneumococcus.

No. 4.—Cultures of pneumococci obtained from urethral discharges of chronic cases of gonorrhœa.

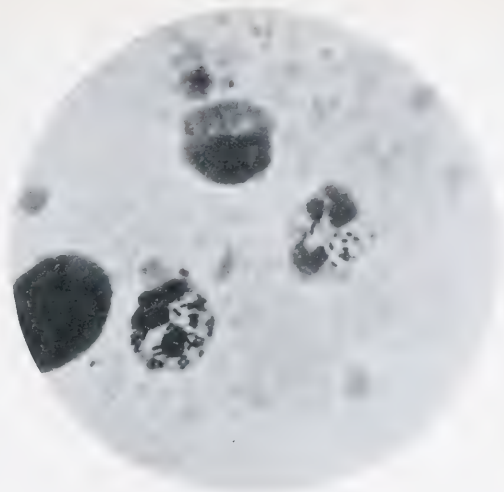
No. 5.—Shows the corresponding smears of the urethral pus from which the cultures shown in No. 4 were obtained.

PLATE VIII

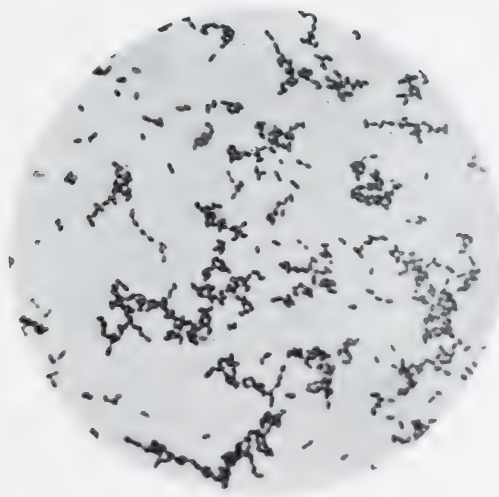
Nos. 1, 2, 3, and 5 are magnified 1000 diameters. No. 4 is natural size.



No. 1.



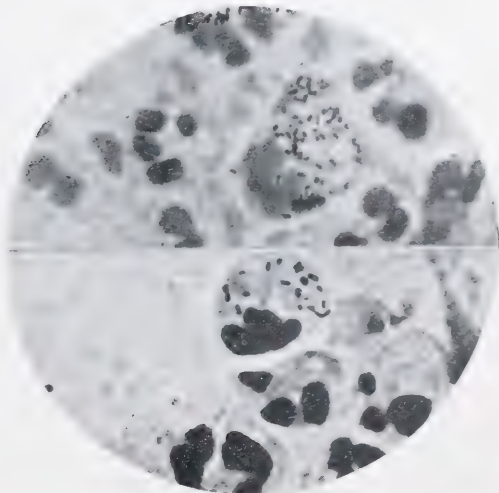
No. 2.



No. 3.



No. 4.



No. 5.

EXPLANATION OF PLATE IX

No. 1.—Urethral smear from a case of chronic gonorrhœa; Gram's stain. Note the strepto-pneumococci lying extracellularly.

No. 2.—Culture of urethral strepto-pneumococci obtained from the same case as No. 1.

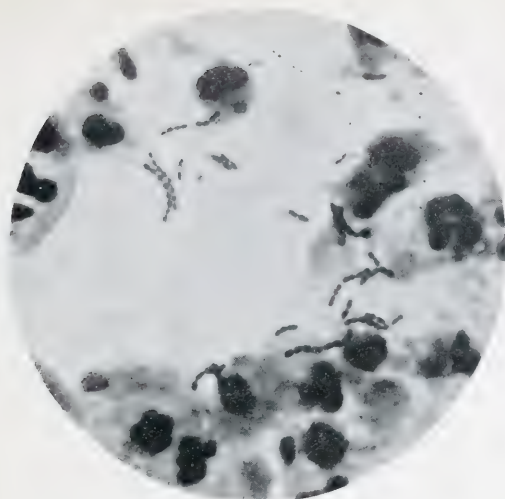
No. 3.—Smear obtained from the water of condensation from the culture tube No. 2. Note the lanceolate shape of the diplococci in the long chains.

No. 4.—Smear from a similar culture obtained from a case of chronic gleet.

No. 5.—Smear from a culture of a true streptococcus obtained from a case of chronic gonorrhœa. Note that the cocci in this case are definitely round and not lanceolate in shape.

PLATE IX

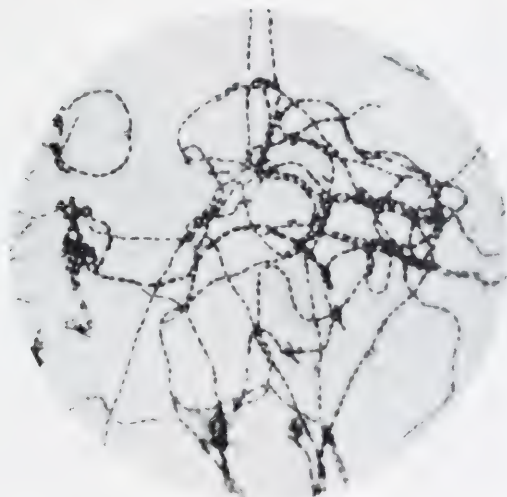
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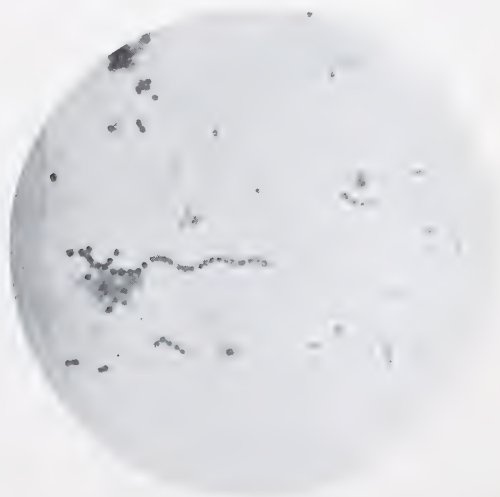
No. 2.



No. 3.



No. 4.



No. 5.

EXPLANATION OF PLATE X

No. 1.—Urethral smear from a case of chronic gonorrhœa; Gram's stain. Note the Gram-negative coliform bacilli lying with a pus cell.

No. 2.—Smear from a culture obtained from the same case as smear No. 1.

No. 3.—Smear from a culture of a coliform organism obtained from another case of chronic gonorrhœa. Note that the Gram-negative bacilli in this case are of a much shorter type.

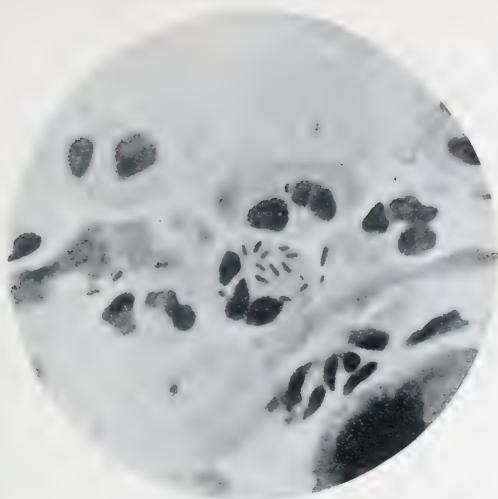
No. 4.—Smear from a culture of a small Gram-negative bacillus obtained from the same case as No. 3.

No. 5.—Urethral smear from a case of chronic gonorrhœa, showing a heavy secondary infection with a small Gram-negative diplobacillus.

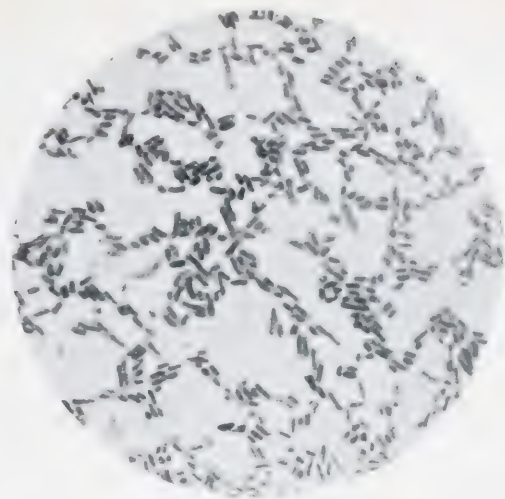
No. 6.—Smear from a culture taken from the same case as No. 5. Note the bacillary and coccoid forms of the Gram-negative diplobacillus. The diplococcal forms are liable to be mistaken for gonococci.

PLATE X

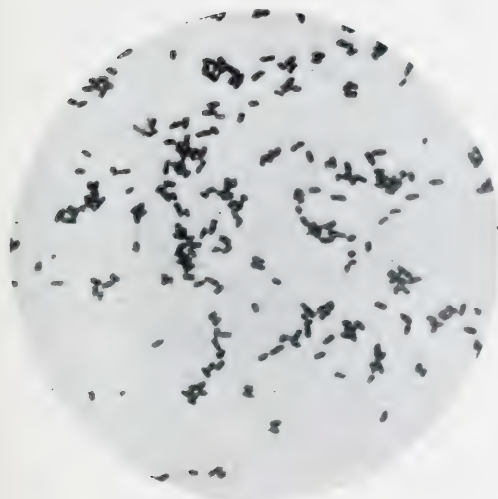
All the microphotographs show a magnification of 1000 diameters.



No. 1.



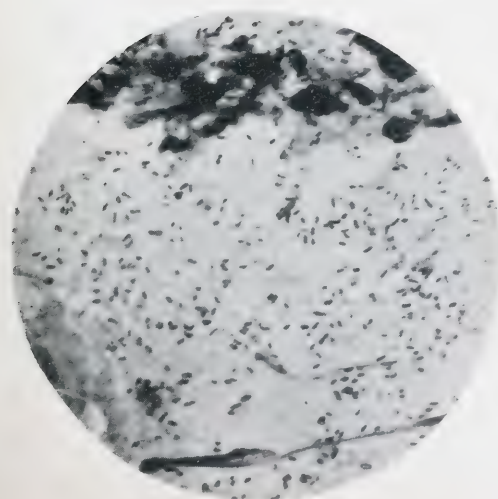
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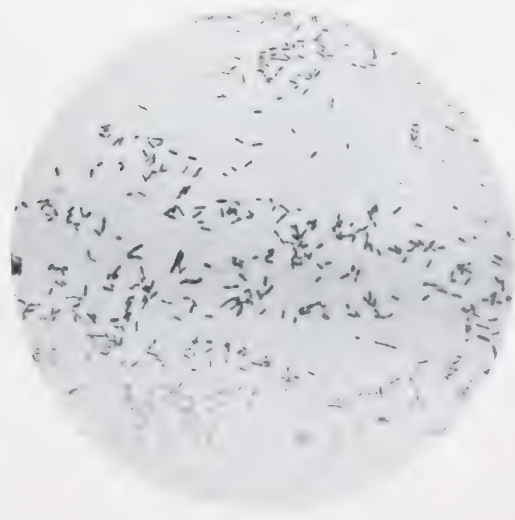
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No. 5.



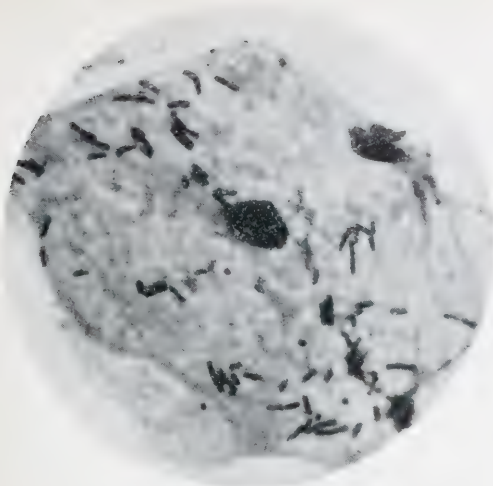
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EXPLANATION OF PLATE XI

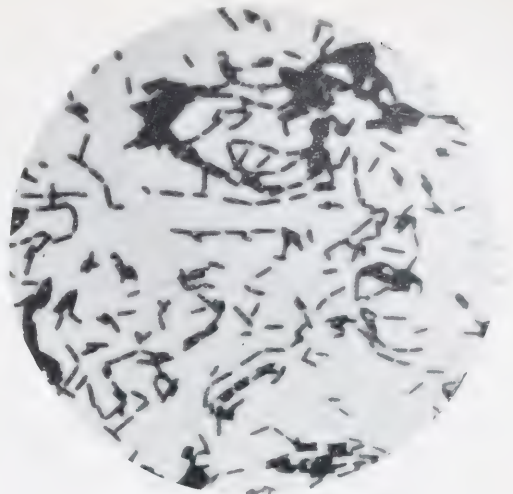
- No. 1.—Urethral smear from a case of chronic gonorrhœa. Note the large epithelial cell, containing Gram-positive bacilli, of an unknown variety.
- No. 2.—Smear from a culture taken from the same case as No. 1. Note that the bacilli tend to form chains, thereby differing from the diphtheroids shown in Plates VI. and VII.
- No. 3.—Urethral smear from a case of subacute gonorrhœa. Note the pus cell containing curved Gram-negative threads of an unknown nature.
- No. 4.—Smear from a culture of a curious Gram-positive diphtheroid obtained from a case of chronic gonorrhœa. Note the great diversity in form of this organism.
- No. 5.—Smear obtained from a case of chronic gleet after prostatic massage. Note the spermatozoa and a curious Gram-negative branching mycelium.
- No. 6.—Smear from a culture of a Gram-negative streptothrix, obtained from the same case as No. 5.

PLATE XI

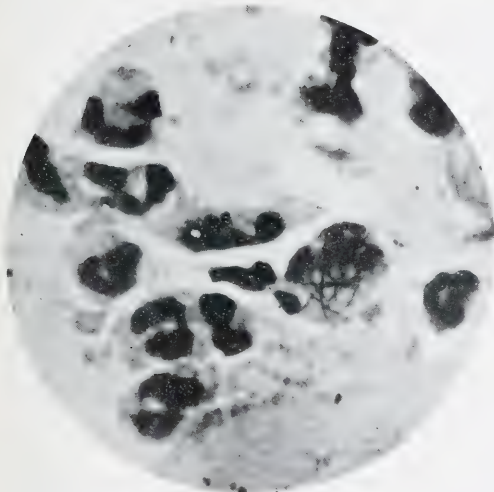
All the microphotographs show a magnification of 1000 diameters.



No. 1.



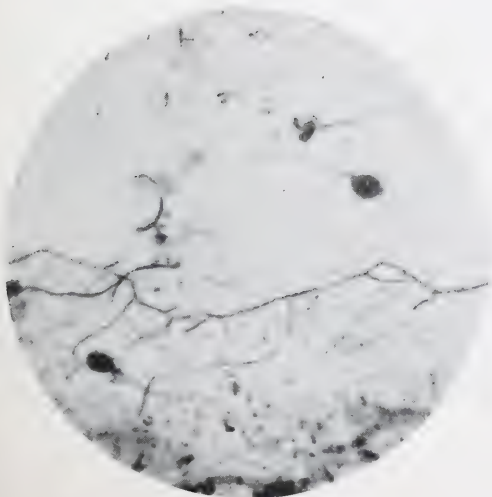
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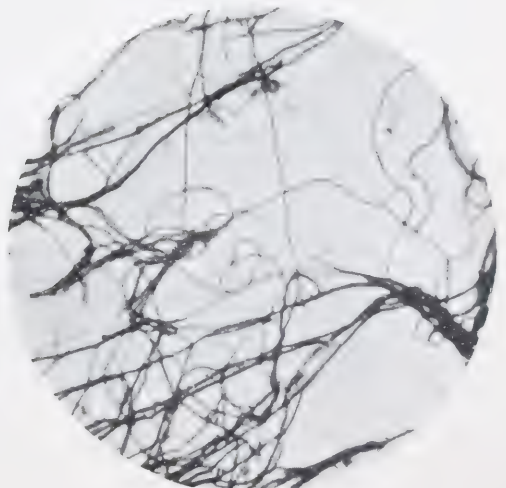
No. 3.



No. 4.



No. 5.



No. 6.

CHAPTER XVI

NON-GONOCOCCAL URETHRITIS

PRIMARY NON-GONOCOCCAL INFECTION—INFLUENCE OF SYSTEMIC DISEASE—INFECTIVITY OF NON-GONOCOCCAL INFECTIONS—URETHRITIS DUE TO ORGANISMS RESEMBLING THE GONOCOCCUS—"ASEPTIC URETHRITIS"—CHEMICAL URETHRITIS—URETHRITIS FROM SPECIFIC DIATHESIS—TOXIC URETHRITIS—TRAUMATIC URETHRITIS

Primary Inflammation of the Urethra due to Organisms other than the Gonococcus.—Although the vast majority of purulent discharges from the urethra and vagina are gonorrhoeal in origin, yet one must never forget that cases occur which are due to other causes. In every instance it is necessary to examine first a Gram-stained smear of the discharge. If no gonococci are found one would then proceed to make a culture. Where gonococci are scarce, however, and difficult to find, the most delicate and reliable means of diagnosis is the complement-fixation test. It is often very difficult to detect gonococci by smear or by cultural methods, more especially in the case of vaginal discharges in females, where the condition is complicated with enormous numbers of secondary organisms. In such circumstances one will often obtain a strong positive reaction by the blood test, where both smears and cultures gave negative results. When, however, the presence of the gonococcus cannot be detected either by smear, by culture, or by the blood test, it is necessary to look for other causes.

There can be no doubt that a urethritis may be due primarily to organisms other than the gonococcus. The author has seen several cases. Usually there is a history of connection, perhaps two or three weeks before the commencement of the trouble. The discharge may be scanty but definitely purulent. Large numbers of staphylococci and diphtheroids are generally found lying within and amongst the pus cells. In at least two cases the presence of gonococci was definitely excluded by examination of smears, by culture, and by the complement-fixation test. Such a urethritis may occur in persons who have never suffered from gonorrhœa. On the other hand, the majority of cases occur in those who have had this disease and in whom, although cured, the mucous membrane is delicate and susceptible to attack by common pyogenic organisms.

A common cause of ordinary pyogenic infection of the urethra is the use of an irritating injection which damages and weakens the mucous lining, and may introduce at the same time outside organisms. For example, a patient who had exposed himself to risk of infection immediately injected a solution of lysol as a prophylactic measure. The solution was sufficiently strong to cause considerable irritation. Next day he had a very profuse purulent discharge, with frequency and pain on micturition. A microscopic examination showed an enormous infection, with large staphylococci lying within and around the pus cells. No gonococci were detected. Cultivation revealed a pure growth of *Staphylococcus albus*, and the complement-fixation test was negative to gonorrhœa. The infection spread upwards and produced a cystitis.

It is necessary to avoid confusing a urethritis with a true cystitis or pyelitis. In the latter condition, of course, the urine is purulent and full of shreds, but there is no definite

discharge from the urethra. Sometimes, however, the latter may also be involved as part of the infection. In true pyuria in the female where there is pyelitis with a urethritis, the most common causal organism is the *Bacillus coli*. There is often, however, a mixed infection with other germs, such as *Staphylococcus albus* or *aureus*, *Streptococcus brevis*, and *Bacillus pyocyaneus*. Next to the *Bacillus coli*, the most common cause of pyuria is the tubercle bacillus.

Again, one must always be on the look-out for intra-urethral chancres. In these there may occur a scanty discharge. Suspicion is aroused in such cases by the detection of definite induration on digital examination and by urethroscopic examination.

Macfie (1917) described a case of acute urethritis in a native of the Gold Coast which he considered was due to infection with a species of spirochæte.

Faroy (1918) reported on a case of orchitis, urethritis, and cystitis occurring in the course of a general infection with *B. coli*.

Rovsing, T. (1918), reported on a case of *B. coli* infection of the prostate, seminal vesicles, and epididymides. He considered that this case was due to an infection from the intestine through the blood stream. There was no history of gonorrhœa.

van der Bluyt and Haay and Besson have recorded similar cases of non-gonorrhœal urethritis. Sometimes they are caused by staphylococci, streptococci, or due to genital herpes.

Dogs and other animals occasionally suffer from a urethritis. Numerous types of germs are found in the discharge, but never gonococci.

Non-Gonococcal Urethritis accompanying or following upon Systemic Diseases.—Primary cases of urethritis may follow certain systemic diseases. Legrain (1889) describes a case following after typhoid fever and from which he isolated the *Micrococcus pyogenes aureus*. Gravis and Stiévenard, Billoir (1859), and Schmitt (1883) cite cases occurring in the course of attacks of mumps. Moscato (1890) had a patient of sixty years of age who developed a discharge from his urethra every time he had an attack of intermittent fever, and which invariably disappeared after the attack.

Kidd (1917) cites two cases of urethritis, each of which occurred during an attack of measles. The discharge in both cases showed pus cells but no organisms. The condition in each case cleared up rapidly without any local treatment.

Panton (1917) states that occasionally urethritis may be due to the streptococcus and the influenza bacillus. More commonly it is due to coliform organisms which may produce an ascending infection of the urinary tract, following sexual intercourse.

The Infectivity of Non-Gonococcal Urethritis.—Legrain (1888) relates an interesting case of a student who developed a greenish urethral discharge twenty-four hours after connection with a woman who had been treated for a retro-uterine abscess two months before. His discharge showed a heavy infection with *Micrococcus cœruleus albus*.

Janet (1893) described two female cases who developed inflammatory lesions after their marriage. In both cases the husbands were found to be suffering from a non-gonococcal urethritis. The infecting organism in all cases proved to be a short bacillus.

Luys (1917) states that non-gonococcal cases of urethritis may be infectious. They are apt, moreover, to cause serious complications in the male, such as epididymitis, prostatitis, and vesiculitis. Such cases may be primary, but more often they are secondary to gonococcal infections. He further states that in the female, as a rule, non-gonococcal infections cause only slight inflammation, usually a mild metritis.

He reports on a case (male) who got a profuse and persistent non-gonococcal urethral discharge after connection with his wife, who had developed leucorrhœa after miscarriages. Also he cites the case of a medical man who developed a streptococcal urethritis after connection with a woman who had suffered from erysipelas. Kidd (1917) cites three examples of non-gonorrhœal urethritis in the male following upon coitus about the time of menstruation. In two of these he found a minute extracellular diplococcus, while the third showed only pus cells and staphylococci. In a fourth case of urethritis which

followed rectal coitus he found an intestinal organism of the proteus group. The patient's serum, moreover, agglutinated this organism in a dilution of 1 in 100. He cites also 3 cases of spontaneous urethritis due to the colon bacillus in adult males, who were over-worked and in a low state of health. The discharge in each case showed pus cells and the *Bacillus coli*. He inclines to the view, however, that non-gonorrhoeal urethral discharges, such as old gleans due to staphylococci and *Bacillus coli*, are non-infectious. He cites a case of staphylococcal urethritis and prostatitis in a man who did not infect women, and also 3 cases infected with *Bacillus coli* whose wives never developed any trouble. On the other hand, he mentions a case where a husband got a *Bacillus coli* urethritis from his wife, who was suffering from a coli infection of the urinary tract.

There can be no doubt that all these germs are primarily far less dangerous than the gonococcus so far as their infecting power is concerned. Nevertheless, as already stated, no man or woman discharging large numbers of such organisms can be regarded as healthy or entirely non-infectious. These germs, apart from the gonococcus, are undoubtedly interchangeable between the genital tracts of males and females, and it has already been shown in Chapter XIV. that the normal and abnormal flora occurring during and after gonorrhoea in the male and female is almost identical in both sexes. These secondary organisms cause much trouble, especially in parts weakened or damaged by the gonococcus, and moreover they may be exceedingly difficult to eradicate.

Cases of Urethritis due to Organisms resembling the Gonococcus.—Gurd (1908) states that it is generally recognised that the *Micrococcus catarrhalis* is responsible for certain forms of catarrhal inflammation of various mucous membranes, including the male and female genitalia. He cultivated this organism from the female vagina in 4 out of 113 cases.

Ayres (1912) maintains that the *M. catarrhalis* is responsible for a definite proportion of cases of urethritis, and Buck (1912) described a case of a urethral infection with this germ, resembling true gonorrhoea.

Thomas, Ivy and Birdsall (1914), employing the complement-fixation test, got a weakly positive result in 10 per cent of gonococcal sera, when they used an antigen of *M. catarrhalis*. They considered this to be evidence in favour of *M. catarrhalis* infections of the urethra, but they appeared to overlook the possibility that these positive results may have been due to nasal and bronchial infections with this organism.

With regard to the meningococcus, Zupnik (1906) showed in 5 cases that this organism did not cause inflammation of the urethra. Reuter (1905), however, described a case of periorchitis in a case of cerebro-spinal meningitis, and von Stabsarzt and Kutscher (1909) state that this organism has been found in the seminal vesicles.

Barnett (1916) got several acute cases of gonorrhoea to react to meningococcus vaccine. This, however, is no proof that some acute cases of urethritis are due to the meningococcus. It may only indicate that this organism is very closely allied to the gonococcus, as is also borne out by the complement-fixation test (see later). There are no doubt strains of gonococci very closely allied to the meningococcus, which form connecting links, so to speak, between the two species. The author agrees with Barnett that the genealogy of the two organisms must be the same.

Urethritis due to the meningococcus and *M. catarrhalis* must be very rare, since out of several hundreds of cultures the author has never succeeded in isolating either of these organisms from the male urethra or urine.

Warden (1913) attempted to show that the majority of intracellular Gram-negative diplococci found in acute gonorrhoea were not gonococci but staphylococci, and that the latter were largely responsible for the disease. Crabtree (1914) showed, however, that Warden's observations were entirely erroneous and fallacious.

The author has occasionally isolated, from cases of chronic gonorrhoea in the male and also in the female, a very short thick Gram-negative bacillus which tends to go in pairs. This organism appears to belong to the *B. coli* group, and may possibly on rare occasions

produce a primary urethritis by itself. It grows very much more profusely than the gonococcus.

So-called "Aseptic Inflammation of the Urethra."—Sometimes one meets with a case wherein the urethral discharge contains no gonococci or other micro-organisms, but only leucocytes and epithelial cells. Such cases have been cited by Noguès (1908), Guiard (1898), and others. The pathology of this condition is still obscure.

Luys states that the condition is always brought on by excessive drinking and exercise, or by excessive sexual intercourse. The condition is more likely to follow after long connections, especially at the time of the menses. The incubation period is usually more than eight days, sometimes three weeks. The onset is torpid and not painful. The discharge is yellowish or yellowish-white, never greenish, and never so profuse as in genuine gonorrhœa. There is very little pain or burning, and the urine is usually clear except for a few small shreds in the first glass. Luys never found gonococci in the women accused, but usually they had a metritis or a salpingitis. He never knew of a case contracted from a completely healthy woman. He states that they are readily cured by silver nitrate injections. They are slow to develop and slow to go. Usually the anterior urethra alone is affected, and the condition is located chiefly in the Littre's glands.

The author has seen such a case in a medical man. He gave a history of a slight intra-urethral induration with a slight discharge, both of which developed six weeks after the last connection. No *Spirocheta pallidum* could be detected on several examinations, and repeated Wassermann tests were all negative. Moreover, smears of the pus, which was yellowish in colour, showed no signs of any organisms whatsoever, and cultures remained sterile. The complement-fixation test for gonorrhœa was also negative.

Cases such as these, discharging apparently sterile pus, must not, of course, be confused with tubercular infections of the genital tract. Nor must they be confused with cases of gonorrhœa under treatment. One often finds an apparently sterile discharge of pus in cases of genuine gonorrhœa which have been irrigated for several days, and from which the gonococcus has at least temporarily disappeared.

Amongst the aseptic cases of urethritis may also be included those inflammatory conditions secondary to strictures, papillomata, polypi, etc.

Chemical Urethritis.—Quite frequently cases are encountered in which there is a considerable discharge of pus containing no gonococci, and which may or may not be free from the common secondary organisms, such as staphylococci, etc. On questioning such patients it will often be found that, after connection, they injected a strong solution of potassium permanganate, or some other chemical, for prophylactic purposes. Next morning they noticed a purulent discharge, and hurried to the doctor in the belief that they had contracted gonorrhœa. The cause of the condition, of course, was the intra-urethral injection of too strong a solution. The complaint, as a rule, clears up quickly if the injections are stopped. Some cases, however, pass on to a septic urethritis, because of the infection of the damaged mucous membrane with staphylococci, etc.

In the treatment of genuine gonorrhœa, moreover, by injection or irrigation a chemical irritation may arise, which keeps up the discharge even after the gonococci have been destroyed. In other words, the gonorrhœa is cured, but is followed by a chemical urethritis. Oxycyanide of mercury is especially liable to cause this condition. In the treatment of gonorrhœa, therefore, one should control the amount of irrigation according to the microscopic findings. When it is noted that the gonococci have disappeared, while abundance of sterile pus continues to be discharged, then it is time to reduce the number and strength of the injections or irrigations.

Urethritis due to Specific Diathesis.—According to Luys this is very rare. It may occur, however, in the following conditions:—

(a) Rheumatic fever.—A case is described by Martineau, quoted by Turbur (1887), wherein a boy, age 14, during attacks of subacute articular rheumatism, always developed a profuse

purulent urethral discharge, which disappeared when the rheumatism ceased. This boy had three such attacks.

(b) Persons subject to arthritis, herpes, and gout are liable to urethral irritation; at any rate, they are predisposed to urethritis.

(c) According to Hamonic (1908) a non-infective urethritis may occur in diabetes. He had a case of this nature in a young subject with glycosuria, in whom the discharge cleared up when put on anti-diabetic diet. In the following years the urethritis recurred each time the glycosuria reappeared. He suggests that the condition may be due to germs developing in the sugary urine under a long prepuce, or due to the direct irritating effect of the diabetic urine on the urethra.

Inflammation of the Urethra due to Toxins.—In certain susceptible persons the urethra may be irritated shortly after the eating of certain vegetables or fruits such as asparagus or strawberries. Schenck mentions a man who developed a urethral discharge every time he ate cress, and Harrison observed a patient who had a copious discharge which lasted five days after eating asparagus freely. Cantharides taken internally may cause cystitis or urethritis. Lallemand describes a case of urethral inflammation following upon a dose of 30 grains of potassium nitrate. Mercier has observed similar cases after the administration of potassium iodide. Savignac, Delacour, and Saint-Philippe also described cases of urethritis apparently caused by the administration of arsenical preparations.

Inflammation of the Urethra due to Trauma.—Urethritis may be caused by the passage of or insertion of foreign bodies into the urethra. The frequent use of a catheter will cause it. Such inflammation may also arise from sexual excesses and masturbation. It may occur also from the irritation arising from phosphaturia or oxaluria.

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CHAPTER XVII

THE BACTERIOLOGY OF PUERPERAL FEVER, PELVIC INFLAMMATORY CONDITIONS AND VULVO-VAGINITIS OF LITTLE GIRLS

PUERPERAL FEVER—PELVIC INFLAMMATORY CONDITIONS—STERILITY—BLINDNESS—
VULVO-VAGINITIS OF CHILDREN

Puerperal Fever.—Gurd states that since 1847, when Semmelweis in Vienna, and, soon after, Holmes in America, proved clinically that there was a definite relationship between certain forms of uncleanness and the incidence of puerperal fever, there has been a more or less constant advance in our knowledge of the various micro-organisms capable of inducing inflammatory conditions of the female pelvis. Practically all pathogenic micro-organisms have been isolated at one time or another by different investigators.

The relationship, too, between the presence of pathogenic micro-organisms in the vagina of the pregnant woman and the onset of post-partum fever has interested many observers. The results of a series of experiments and investigations carried out by various writers have, however, been far from satisfying. Opinions regarding the importance of and the frequency with which the gonococcus is met with in disease of the female genital tract are by no means uniform. For the most part this difference of opinion appears to be due to insufficient methods for the detection of this diplococcus.

Krönig (1893) in an investigation of 179 cases of puerperal fever obtained streptococci in 41·9 per cent, anaerobic bacteria in about 18 per cent, and gonococci in about 27·9 per cent.

Czerniewski found streptococci in 53·8 per cent of 91 cases, whilst Whitridge Williams obtained streptococci in 29·4 per cent of 150 cases and gonococci in 5·4 per cent.

Vogel got streptococci in 29·1 per cent out of 24 cases.

Kuehnan records a case of puerperal fever which died with *B. tetani* in the uterus, and another case with the bacillus of malignant œdema. The *B. aerogenes capsulatus* has also been found.

Foulerton and Bonney (1905) examined 54 cases of the disease. Forty cases were severe and the other 14 were mild. Bacteria were found in 35 out of the 40 severe cases and in 4 out of the 14 mild cases. Streptococci were found in 25 of the severe types. In 10 of these they were present in pure culture. In the remaining 15 cases they were in company with other organisms. They therefore found streptococci present in 46·2 per cent of their series. In 1 case they obtained a pure culture of pneumococci. In 2 others a similar diplococcus was found, and in other 3, pneumococci mixed with other bacteria were cultivated. *Staphylococcus albus* frequently occurred as a secondary infecting organism. This latter organism occurred alone in 1 mild case. A diphtheroid bacillus was found in 2 severe cases. *Bacillus pyocyaneus* was obtained in 2 cases, accompanied by streptococci in the one and by *B. coli* in the other. Anaerobic bacteria were only found in 1 case, and this was apparently a secondary infection. They did not

find the gonococcus in a single case, but from 2 cases, 1 mild and 1 fatal, they cultivated a Gram-negative diplococcus, which grew on ordinary agar and did not liquefy gelatin.

Shaw (1917) states that streptococci were most commonly found in puerperal fever either alone or accompanied by *Staphylococcus albus*, pseudo-diphtheria bacilli, or *B. coli communis*. He found streptococci in the blood in about 5 per cent of all cases. The type of streptococcus found in most cases was the *Streptococcus brevis* in chains of three to six cocci. The *Streptococcus longus* occurred only in a few cases. He thinks that these organisms may get into the uterus from the outside through carelessness, or they may have been already in the vagina or cervix during pregnancy. He quotes Burgubru and Williams as having proved the latter contention. *Staphylococcus pyogenes aureus*, according to Shaw, only causes puerperal fever very rarely. A few cases of a pure *B. coli communis* infection have been recorded, but these cases are distinctly rare and usually mild. Shaw, however, had a fatal case. He states that it is, however, a frequent cause of secondary infection. The proteus group is said to be a primary cause, but this has not been definitely proved. Finally he mentions a case infected with the true *B. diphtheriae* recorded by Haultain which recovered after a dose of anti-diphtheritic serum.

Lowenstein (1907) observed in 6 cases that a latent gonorrhœa in women became acute owing to parturition, and thereby gave rise to a fresh attack of gonorrhœa in the husband.

Gurd (1908) states that the importance of the gonococcus as a factor in pelvic disease, and especially in puerperal fever, is greatly underestimated. The gonococcus is extremely prevalent among women attending hospital gynæcological clinics; at least 50 per cent suffer from this infection.

The lesions produced by it may become extremely chronic, viable organisms being found years after any history of active disease can be obtained. The occurrence of pregnancy and labour is often sufficient to induce an active pathogenic development upon the part of these apparently non-virulent dormant organisms. The gonococcus is frequently a predisposing factor to a more serious infection, such as with the streptococcus.

Smith (1911) described a severe case of puerperal sepsis due to a gonococcal infection.

Jaeger (1913) contributed a paper on "Gonorrhœa in relation to Pregnancy and the Puerperal Period," but the author has been unable to gain access to his work.

Hanner (1913) states that an old or latent gonorrhœal infection is liable to flare up and spread after delivery, and that this is a most cogent argument against allowing women to leave their bed soon after childbirth. It is very important to detect the cases which have gonorrhœa before delivery. He found gonococci in 4 per cent of 1753 pregnant women. He states that this does not reveal all of the cases, since some supposed to be free were allowed up at the usual time and the temperature went up suddenly. Gonococci were then found in the lochial discharge. He maintains that if there is any suspicion of gonorrhœa, internal examinations should be scrupulously avoided, and the patient should be kept absolutely quiet in bed for at least two weeks.

From the literature therefore it would appear that many cases of puerperal fever are due to streptococci, and that many are not gonorrhœal in origin. It should be remembered, however, that these infecting organisms may have gained access to the female genital tract during an attack of gonorrhœa, so that indirectly gonorrhœa might be responsible for a larger number of cases than has hitherto been suspected. This could only be ascertained by doing the complement-fixation test in a large series of cases.

Inflammatory Pelvic Infections.—In these there is more evidence that the gonococcus plays a very important rôle.

Norris (1913) gives the following table of opinions by various observers as to the

percentage of cases of pelvic inflammatory infections which are due to the gonococcus:—

Price	90 per cent	} Percentage of pelvic infections due to the gonococcus.
Norris (1913)	80 "	
Pozzi and Frederic	75 "	
Clark	50 "	
Davis and Noble	5 to 10 "	
Robb	25 "	
Grandin	60 "	
Kaan (1912)	5 to 10 "	

Gurd (1908) found gonococci by culture methods in 55 per cent of pelvic inflammatory diseases in women, and in 72 per cent of all cases diagnosed as probably gonorrhœal. In 50 per cent of all women presenting themselves at a good class clinic he was able to find gonococci.

With regard to inflammatory conditions of the Fallopian tubes and ovaries Norris gives the following percentages of bacteriological findings by three different observers:—

Andrewes (1904).	Menge (1910 ?), 106 cases.	Krönig (?), 122 cases.
43 % Gonococci.	64 % Sterile.	61 % Sterile.
24 % Streptococci and staphylococci.	21 % Gonococci.	23 % Gonococci.
5 % <i>B. coli</i> .	8 % Tubercle bacilli.	7 % Tubercle bacilli.
4 % Pneumococci.	4 % Streptococci.	3 % Pyogenic.
1·3 % Tubercle bacilli.	0·96 % Staphylococci.	
	3 % Anaerobic bacilli.	

Gurd (1910) believes that 80 per cent of all cases of salpingitis are gonorrhœal in origin. Old chronic purulent cases, however, may become a nidus for infection with other organisms such as the colon bacillus.

Neisser, Bumm, and Fürbinger state that 40 per cent of all females infected with gonorrhœa suffer from pelvic symptoms.

Norris (1913) believes that certainly 50 per cent of all pelvic infections in the female are undoubtedly due to gonorrhœa.

Kaan (1912), on the contrary, believes that statements which claim that gonorrhœa in women is responsible for 60 per cent or more of the operations for pelvic inflammation are decided exaggerations and should be modified in the interest of truth and proper teaching.

Bowers (1915) maintains that the gonococcus is the primary cause of the majority of pelvic infections, but that it is a single infection for a very short time, not more than two or three days, so that the cases become complicated with staphylococci, *B. coli*, and streptococci.

De Bovis (1912) analysed the opinions of various authorities on the ætiology of salpingitis and pyosalpinx. M. Pankow, professor of the gynecological clinic at the University of Fribourg im Breisgau, maintained that the cause of pyosalpinx was as follows:—

- 43 % were of gonococcal origin.
- 22 % were due to affections of the appendix.
- 22 % were of tubercular origin.
- 13 % were puerperal (streptococcal).

De Bovis disagrees with these figures, and considers that a much higher percentage are due to gonorrhœa, and that very few are due to appendicitis. He points out that Schridde (1910) out of 280 cases of pyosalpinx had not found a single case to be due to appendicitis. Moritz (1912) examined 44 cases of suppurating tubes, and concluded that not one of them was due to previous appendicitis.

De Bovis also considers that Pankow's tubercular percentage is also too high, and points out that M. Labhardt (1912) puts the figure at 11·5 per cent.

Heynemann (1912), on the bacteriological findings in 17 cases, obtained the following results :—

58·8 % gonococcal.	} On 88 cases this author gives the following figures based on clinical evidence :—	65·9 % gonococcal.
23 % streptococcal.		25 % streptococcal.
5·8 % staphylococcal.		6·8 % tubercular.
11·7 % tubercular.		1·1 % due to appendicitis. 1·1 % due to other causes.

De Bovis is inclined to agree with the figures given by Wertheim, Schridde and Menge. Wertheim states that 82 per cent are gonococcal, and Schridde puts the gonorrhœal cause as high as 88 per cent. Menge gives the following percentages, which conform closely to those of Schridde :—

85 % gonococcal.
10 % tubercular.
5 % due to pyogenic bacteria.

Schwartz and McNeil (1911) obtained the following results with the complement-fixation test in 59 gynæcological cases : 44 per cent negative, and 56 per cent positive.

Out of 30 cases with no signs or history of gonorrhœa 33 per cent of positive results were obtained.

Rockwood (1914) obtained positive results in 50 per cent of 8 cases examined by this test. Now that the complement-fixation test has reached a higher state of perfection and delicacy, it is likely that further investigations by the newer methods will give an even higher percentage of positive results.

There is no doubt that the complement-fixation test carried out in a large series of cases would help to elucidate matters very considerably. A certain amount of work has already been done in this respect. Thus Kolmer and Brown (1914), in a few cases of pyosalpinx examined, state that 66 per cent gave a positive fixation reaction to the gonococcus.

Ower (1915) carried out this test in 23 cases of acute and chronic inflammation of the Fallopian tubes. Fourteen, or 61 per cent, were positive reactions and 39 per cent negative. Of these negative cases 4, or about 17 per cent, were found on operation to be tuberculous; one showed both tubercle bacilli and gonococci in smears, and a culture of the latter was obtained. Thus 65 per cent of Ower's cases were apparently gonorrhœal.

Luys (1917) states that it has been established beyond doubt that about 70 per cent of the Bartholinitis, cystitis, metritis and salpingitis met with in married women are due to the gleet of their careless, ignorant or unscrupulous husbands. The words of Jullien (1898), according to Luys, are only too true : "Generally, morbid conditions arise which are of a persistent character, and show no tendency to cure. The generative organs become gradually involved to their whole extent; the general health suffers; all the functions of the body become slack; the women merely drag along, and have to pay with weeks of invalidity for every minute of exertion, for the slightest error in diet, and for a walk of any distance. The home is childless, there is no happiness, and this state of affairs may last for years!"

With all due deference to the opinions of Kaan and others, the author agrees with Gurd, Norris, Luys, etc., that a high percentage of pelvic infections in females, 50 per cent and over, are due to gonorrhœa.

Gurd has pointed out that the diverse results obtained and the difference of opinion as to the prevalence of the gonococcus may be explained by—

(1) The difficulty of isolating and differentiating the gonococcus by culture.

(2) The small number of gonococci which are usually present, especially in chronic lesions.

(3) The presence in the vagina of a multitude of other organisms, several of which are with difficulty differentiated from the gonococcus.

(4) Different methods of procuring material for examination.

(5) Neglect of the value of precise laboratory methods.

The author would also like to point out that the gonococcus very often opens the way for other organisms by damaging the tissues; and although those secondary organisms are easily found, the co-existing gonococci may be missed, as their number may be scanty and they are difficult to cultivate. Finally, if we even admit that other organisms by themselves cause a large percentage of pelvic inflammations in females, how are we to know that the latter were not infected from a chronic gleet in the male, where secondary organisms abound, although gonococci may be absent. If this were the explanation of some cases, these would still be due indirectly to the gonococcus.

At any rate it is much more dangerous to minimise than to exaggerate the prevalence of gonorrhœa. There is not the slightest doubt whatsoever that the disease is exceedingly common, and amongst females many cases remain undiagnosed. The fault in most cases is not one of exaggeration, but rather it lies in the number of cases that are missed.

Prof. Munro Kerr (1922) states that "Puerperal infection is still the commonest cause of salpingitis. I know that others hold a different view and give gonorrhœa the first place."

Sterility.—Neisser, Bumm, and Fûrbinger state that 30 per cent to 50 per cent of all childless marriages are due to gonorrhœa.

Kaan (1912) discredits the statement that 45 per cent of the cases of sterility are due to gonorrhœa. It cannot be denied, however, that gonorrhœal epididymitis is by far the greatest cause of sterility in the male, and this in conjunction with the female cases due to salpingitis must account for a large amount of sterility.

McDonagh (1920) mentions that chronic prostatitis is frequently said to be a cause of sterility, and a cause of enlarged prostate in later life.

Rongy and Rosenfeld (1922) state that, owing to the diminished prevalence of gonorrhœa in the male during the past two years, only 10 per cent of cases of sterility in families applying for treatment is traceable to causes due to the husband, whereas in previous years the figure was as high as 25 per cent. To regard stenosis of the cervical canal as responsible for sterility is fallacious. They tested the potency of the Fallopian tubes in 400 cases of sterility by intra-uterine insufflation of oxygen or carbon dioxide, followed by fluoroscopic examination in the erect posture. Fifty-eight per cent showed the presence of gas in the abdomen, showing that the tubes were clear.

Blindness.—Neisser, Bumm and Fûrbinger maintain that gonorrhœa is responsible for 20 per cent of all the blindness in the world.

According to Edgar (1907), so widespread is blindness from this cause that Magnus, who made careful statistical observations, says that out of 2528 cases of blindness at all ages in Germany, 108 were due to gonorrhœa. In institutions the proportion is much larger, and the Committee of the Ophthalmological Society of Great Britain in 1884 found that 30 per cent of the blindness was due to this disease.

In Mexico, Ramos calculated that out of 6500 cases 30 per cent were due to the gonococcus. Ophthalmia neonatorum occurs in 0.5 per cent of all children born (see also Chap. XXXVI.).

Vulvo-vaginitis in Children.—Most recent observers agree that this condition is usually caused by the gonococcus. Some of the older observers, however, believed that cases of non-gonococcal vaginitis occurred.

Veillon and Halle (1896) describe *B. pseudo-diphtheriae*, streptococci, *Staphylococcus albus*, and rarely *B. coli*. Robertson (1899) found the gonococcus in 41 out of 54 cases of vulvo-vaginitis in children, and Barkenheim (1903) found it in 75 per cent of his cases. Edgar (1907) states that one should always suspect gonorrhœa in a child where there is

a purulent vaginal secretion. If pus be found without apparent bacteria this often indicates the disease.

Wollstein (1907) found the gonococcus to be the chief cause of infantile vulvo-vaginitis. In all cases, as a rule, the germ was easily isolated. Sometimes almost pure cultures were obtained. All of the strains isolated from 10 cases fermented maltose, and they grew easily on ordinary agar. They appeared to differ, therefore, from the usual types found in adults.

Alice Hamilton (1908) states that nearly all chronic cases present the same secondary organisms as are found in old-standing gonorrhœal discharges of adults. The commonest types in order of frequency were *B. pseudo-diphtheriæ*, *Staphylococcus albus*, *Streptococcus*, and *Staphylococcus citreus*.

Sherber (1910) found vibrios and spirochætes in 11 cases with clinical evidence of vulvitis and vaginitis.

Van Gieson (1910) communicated a paper on the "Errors in the Search for the Gonococcus in the Vaginitis of Children,"

Rubin and Leopold (1913) state that gonococcal vulvo-vaginitis in children is very persistent as compared with adults, and that it is very difficult to obtain a cure. They give reasons for this persistence and chronicity.

Kolmer and Brown (1914), also G. G. Smith (1914), found that a large number of cases gave a positive complement-fixation reaction to the gonococcus, and consider this test to be very valuable in aiding the diagnosis and management of the disease. Irons and Nicoll (1915) came to a similar conclusion. They isolated the gonococcus in 12 out of 17 cases. In 7 of these 12 cases the complement-fixation reaction was positive, and it was also positive in 4 of the 5 cases from which no gonococci could be isolated.

Trist and Kolmer (1915) state that in subacute and chronic cases of vulvo-vaginitis with scanty discharge, vaginal washings will disclose gonococci in from 20 to 25 per cent of cases, when direct smears are negative. The percentage of positive findings was also increased after irritation of the vaginal mucosa with silver nitrate after the provocation method of Norris. The absence of gonococci in vaginal washings give, according to these observers, greater assurance of the absence of gonococcus infection than the usual smear examination. Treatment guided by the former method is likely to be more thorough, though greatly prolonged.

Pontoppidan (1915) found that complications occurred in 6.8 per cent of 779 cases of vulvo-vaginitis of infants in the records of a Copenhagen hospital. He does not give any information as to what organisms were found in these complicated cases.

Pearce (1915) maintains that the type of gonococcus found in infantile vulvo-vaginitis is different from that in adults. He found that by suitable immunological tests, viz. agglutination and complement-fixation, the infantile type could be distinguished from the adult types. The strains of gonococci isolated from 3 cases of ophthalmia were found by these tests to belong to the adult type.

Cole and Lloyd (1917) also believe that the cause of infantile vulvo-vaginitis may be a special group of gonococci different from the type which causes the usual gonorrhœal urethritis in adults.

Valentin (1921) relates her experience in the treatment of 161 cases of infantile vulvo-vaginitis. After from 2-4 weeks' treatment the course was suspended if the tests for gonococci were negative, but in almost all of the cases examined after several weeks or a month there was a renewal of the discharge, which was found to contain gonococci. The same treatment as at first caused the discharge to cease and the gonococci to disappear in from 4-8 weeks. If the treatment was interrupted, recurrences set in again. Some children had three or more recurrences, requiring them to be kept at the station for more than a year. The cause for the recurrences was due to the fact that the gonococci in the glands or neighbouring organs were not easily accessible to treatment. In 61 of the children in whom recurrences occurred, gonococci were found to persist in the rectum.

For further information on vulvo-vaginitis see Chapter XXII.

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PART II

THE ANATOMY, PATHOLOGY, MORBID HISTOLOGY, AND CYTOLOGY OF GONORRHOEA—CLINICAL PATHO- LOGY OF LOCAL AND SYSTEMIC INFECTIONS

CHAPTER XVIII

THE ANATOMY OF THE MALE GENITO-URINARY TRACT

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Urethra.—The male urethra commences at the internal urethral orifice of the bladder and ends at the meatus of the glans penis. Its average length is about eight or nine inches. Anatomically it is divided into three parts. The first part passes through the substance of the prostate gland and is termed the *pars prostatica urethrae* (prostatic urethra); the second part, *pars membranacea urethrae* (membranous urethra), is that part contained between the two layers of the urogenital diaphragm or triangular ligament, and enveloped by the muscular fibres of the compressor urethrae muscle; the third part, *pars cavernosa urethrae* (penile urethra), traverses the entire length of the corpus cavernosum urethrae.

Clinically, however, the male urethra is divided into anterior and posterior regions, the anterior urethra corresponding to the *pars cavernosa urethrae*, and the posterior urethra including the *pars prostatica urethrae* and the *pars membranacea urethrae*.

The Anterior Urethra.—The anterior urethra extends from the meatus urinarius to the anterior edge of the triangular ligament (inferior fascia of the urogenital diaphragm). It is the longest part of the urethra, being about six inches long, and is embedded in the substance of the corpus spongiosum, which expands posteriorly into the bulb. The posterior part of the anterior urethra lying between the anterior layer of the triangular ligament and the peno-scrotal junction is termed the *bulbous urethra*, and is about one inch in length. The meatus is the narrowest part of the canal. Just within the meatus is the dilatation called the fossa navicularis; beyond this the canal remains of uniform calibre, until the bulbous urethra is reached, at which part the canal again widens. The anterior urethra is further subdivided into pendulous and fixed regions, the fixed region being attached to the anterior layer of the triangular ligament and to the symphysis pubis by the suspensory ligament of the penis. It is important to note that secretions in the pendulous region will gravitate to the meatus, while in the fixed region they will gravitate posteriorly to expand the bulb, and will only show at the meatus, as an overflow or on forcible expression from behind the peno-scrotal junction.

The *mucous membrane* of the anterior urethra consists of delicate columnar epithelium, except in the fossa navicularis where it is stratified. The epithelium rests upon a vascular

mucous membrane, which is supported by a coating of submucous tissue containing an inner longitudinal layer of plain muscular fibres, and an outer circular layer. Outside this is a close plexus of small veins, which is connected with the corpus spongiosum.

The *mucous membrane* is beset with numerous mucous glands, simple and compound or racemose, whose acini are lined with clear columnar cells which yield a mucous secretion. These gland follicles are termed *Littre glands*, the openings of which are directed forwards towards the meatus. There are also a number of oblique recesses on the roof and lateral surfaces of the canal called *lacunae of Morgagni*. The large lacuna in the roof of the fossa navicularis is called the *lacuna magna* (see Pl. XII.).

The two ducts from Cowper's gland open into the floor of the bulbous portion of the anterior urethra.

The capacity of the anterior urethra varies from eight to fourteen cubic centimetres ($\frac{1}{4}$ – $\frac{1}{2}$ fl. oz.).

Posterior Urethra.—The posterior urethra extends from the anterior edge of the triangular ligament or inferior fascia of the urogenital diaphragm to the urethral orifice of the bladder; it includes the *membranous* and *prostatic* portions of the urethra.

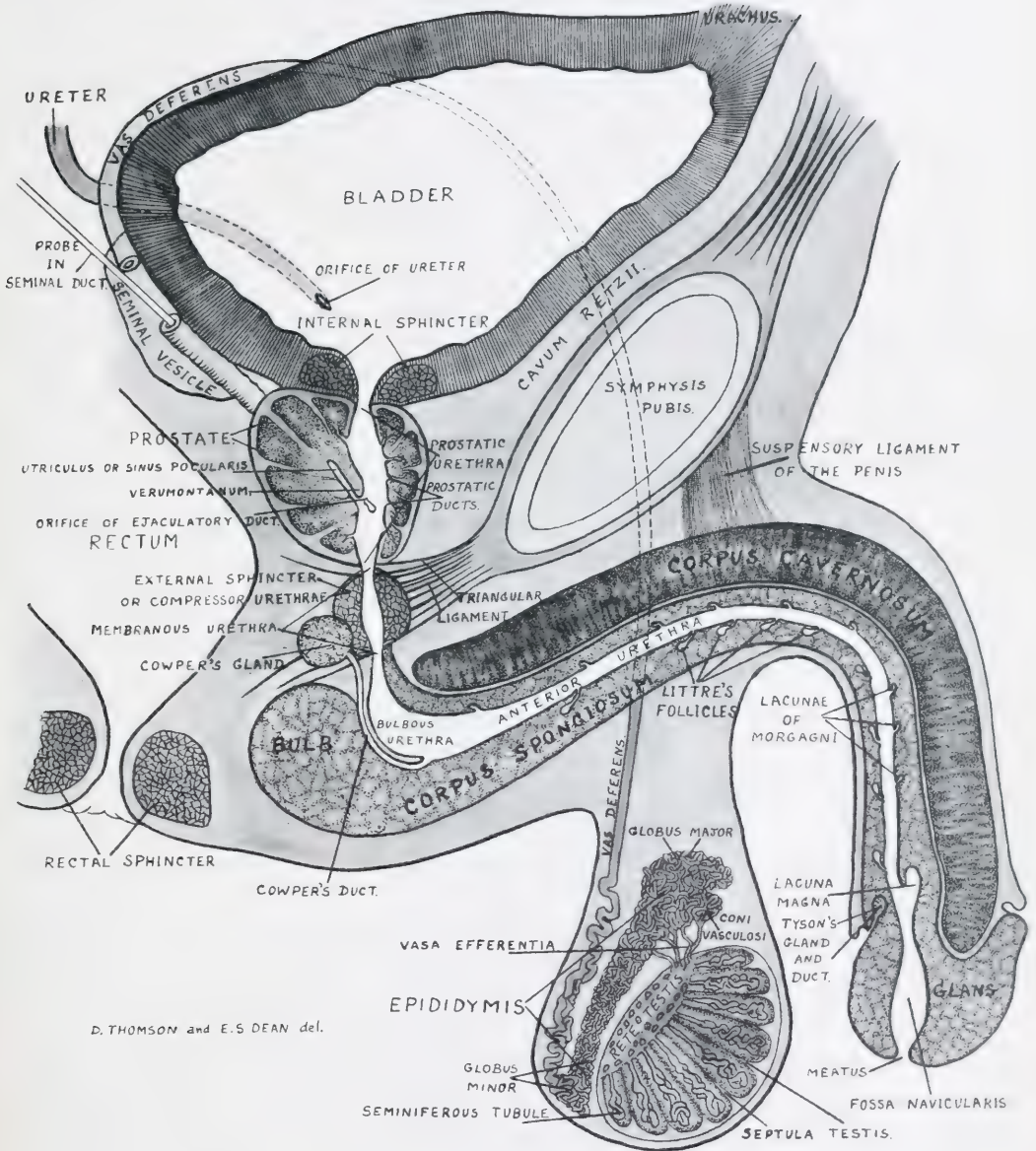
The *membranous portion* (*Pars membranacea urethrae*) lies between the two layers of fascia of the urogenital diaphragm or triangular ligament, and extends from the prostate, piercing the upper fascia of the urogenital diaphragm or posterior layer of the triangular ligament, and terminates at the bulb by piercing the inferior fascia of the urogenital diaphragm or anterior layer of the triangular ligament. It is the narrowest and shortest part of the urethra, being barely three-quarters of an inch in length. The canal curves gently downwards and forwards behind the lower border of the symphysis pubis. The mucous membrane (which is scanty in mucous glands) is directly surrounded by a thin coat of erectile tissue, which is embraced by a muscular coat of involuntary fibres arranged circularly. The compressor urethrae muscle, or *sphincter urethrae membranaceae*, envelops the membranous urethra in its entire length. This muscle is normally in a state of tonic contraction, and consequently cuts off the anterior urethra from the posterior urethra, and is aptly termed the "*cut-off muscle*." Placed behind the membranous urethra are *Cowper's glands* or *bulbo-urethral glands*; they lie one on each side, and their ducts open into the bulbous part of the anterior urethra. They are about the size and shape of a pea, and secrete a clear viscid secretion like the white of an egg, which acts as a lubricant to the urethra, and can be often detected as a clear drop at the meatus on sexual excitement.

Prostatic portion (*Pars prostatica urethrae*).—This part is about one inch and a quarter in length (30 mm.). It is the widest and most dilatable part of the canal, being easily dilatable to 40–45 (French scale). The course of the canal is almost vertical through the substance of the prostate gland.

Mucous Membrane.—The epithelium is of the transitional variety and is similar to that of the bladder. On the posterior wall or floor the mucous membrane is raised to form a narrow prominent ridge called the *crista urethrae*. This ridge commences just below the internal orifice of the urethra in the bladder and extends downwards for about three-quarters of an inch. Upon this ridge is a prominent eminence, termed the *colliculus seminalis* (seminal hillock) or *verumontanum*; from this eminence the ridge gradually decreases.

On the anterior surface of the *colliculus seminalis* the mucous membrane dips backwards and upwards to form a small cul-de-sac within its substance called the *utriculus prostaticus* or the *sinus pocularis*. The orifice of this cul-de-sac is narrow, but widens out towards its blind upper end, and is about one-quarter to an inch in length. This small cul-de-sac of the *utriculus prostaticus* is of clinical importance, in that it may be large enough sometimes to engage the point of a small catheter or bougie. Developmentally it represents in the male the vagina and uterus of the female. On the lateral margins of the orifice of the utriculus, or it may be just within them, are the two minute slit-like orifices of the *ejaculatory ducts*.

PLATE XII



Anatomy of the Male Genitalia.

On each side of the urethral crest is a longitudinal depression called the *prostatic sinus*, upon which open the numerous ducts of the prostate gland (see Pl. XIII.).

Direction of the Urethral Canal.—The *prostatic portion* is directed vertically downwards and slightly forwards.

The *membranous portion* describes a gentle curve behind the symphysis pubis, its concavity looks forwards and upwards.

The *cavernous portion*, in the fixed region, ascends upwards and forwards, while in the pendulous region, in the flaccid condition of the penis, it curves downwards.

The canal of the urethra, with the penis in the flaccid condition, forms a course of two curves, resembling the letter *o* placed upon its side. However, when the pendulous portion of the penis is raised the cavernous part of the canal becomes one large curve, with its concavity directed upwards (see Fig. 5).

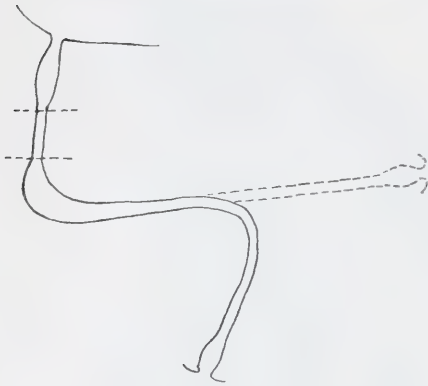


FIG. 5.

Prostata, or prostate gland.—The prostate is a firm, solid body, about the size of a chestnut. It is conical in shape and surrounds the urethra. Its size is variable, but its average length from base to apex is about one and a quarter inches (31 mm.), while its average breadth, at its broadest part, is about one and a half inches (37 mm.).

Position.—Anatomically, the prostate presents a base or superior surface, an *apex* or inferior surface, two *lateral* surfaces, an *anterior* rounded border and a *posterior* surface. The

base is directed upwards, and is in close contact with the bladder. The *apex* is directed downwards, and rests upon the upper fascia of the urogenital diaphragm (posterior layer of triangular ligament). The two lateral surfaces rest upon the *levator ani* muscles. The *posterior* surface rests upon the anterior aspect of the rectum, from which it is narrowly separated by cellular tissue, and can be palpated per rectum. A median vertical groove may be felt—corresponding to the floor of the urethra, and separating the gland into two lateral lobes.

The *anterior* rounded border lies about three-quarters of an inch behind the lower part of the symphysis pubis.

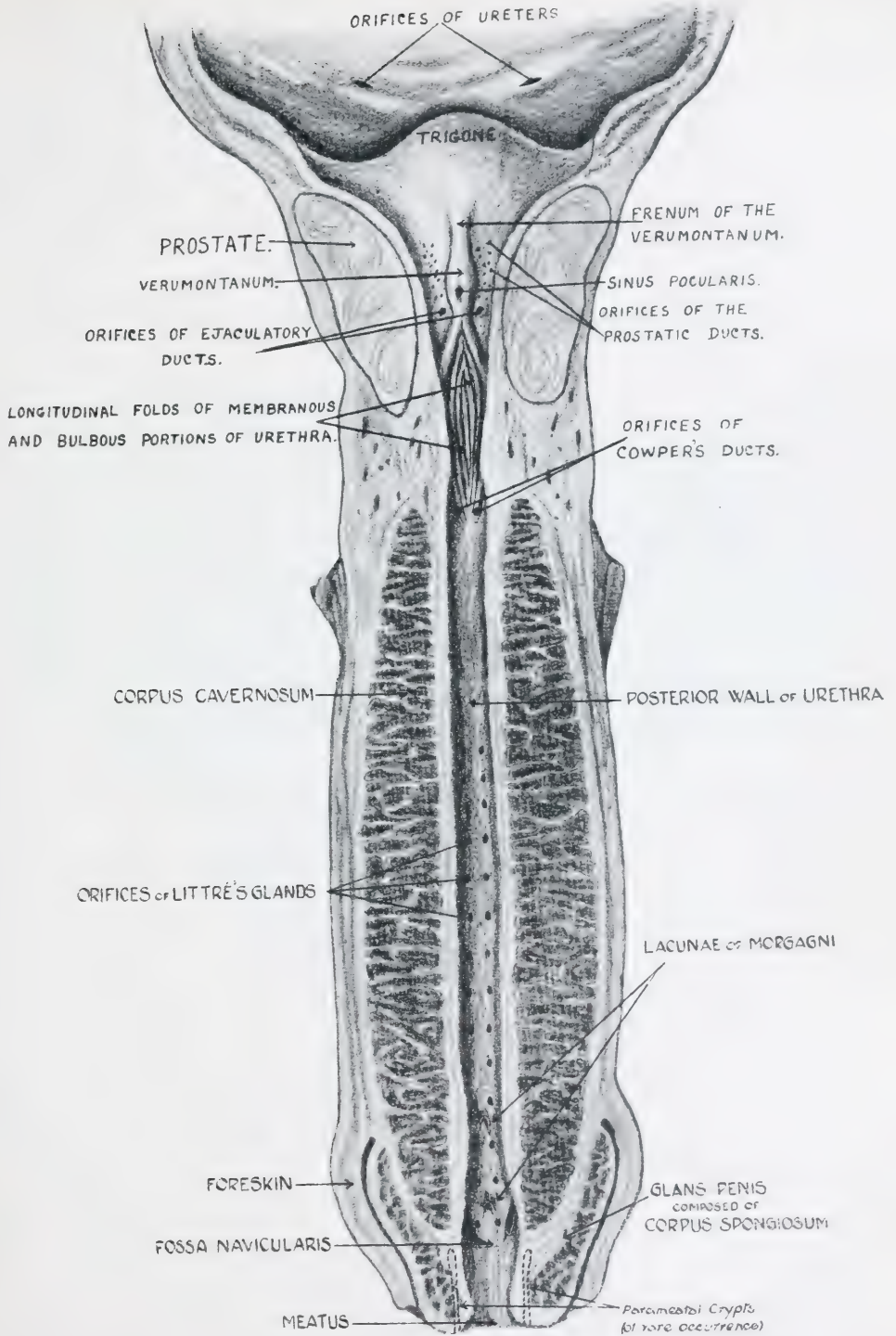
Structure.—The prostate is clothed externally in a thin external fibrous sheath. Within this lies a thin-walled plexus of veins called the *pudendal plexus*, which is spread over the anterior and lateral surfaces of the prostate. Immediately surrounding the prostate is the *inner fibrous capsule proper*. This fibrous capsule varies in thickness, being in some cases only a thin capsule, while in other cases it forms a dense cortex surrounding the gland. The fibrous capsule has very little connection with the venous plexus or the external fibrous sheath, and for this reason the gland can be easily shelled out.

The ejaculatory ducts pierce the base of the prostate a short distance behind the internal urethral orifice. The part of the prostate between the ejaculatory ducts and the bladder and the urethra in front, is the so-called middle lobe of the prostate.

Histology of the Prostate.—The prostate is composed of muscular and glandular tissue. The glands are composed of numerous tubular alveoli, lined with columnar epithelium cells, resting upon a thin basement membrane. Surrounding the alveoli is a musculo-connective tissue. The gland-tissue of the alveoli communicates through numerous duct openings within the posterior urethra, and it is along these ducts that a gonococcal infection may extend into the prostate gland.

Characters of Prostatic Secretion.—The prostatic secretion is a thin, opalescent, albuminous fluid, and has a characteristic odour. It contains no mucus. It is faintly

PLATE XIII



alkaline, but may be neutral, or slightly acid. The secretion microscopically shows lipid granules, and also other granules termed corpora amylacea. Epithelial cells and leucocytes may also be present.

Vesiculæ Seminales.—*Position.*—The vesicles lie against the base of the bladder. They are conical or pyriform in shape, and each is about two inches (50 mm.) long. Each vesicle lies to the outside of the vas deferens, the lower pointed ends rest upon the base of the bladder, and are in close proximity, but separated from each other by the two ducts, the *vasa deferentia*. The vesicles diverge as they ascend upwards and outwards from the base of the prostate, so that the blunt upper ends are widely separated. Each is bound together to the vas deferens, which lies along its inner side, by a dense areolar tissue (see Pl. XIV.).

Each vesicle consists of a tube, five to six inches long, which is convoluted and bent upon itself and bound together by areolar tissue. The lower end of each vesicle terminates in a short duct called the *excretory duct*; this duct joins the vas deferens at an acute angle to form the *ejaculatory duct*.

They produce an alkaline secretion which forms a constituent of the spermatic fluid. The secretion is of a greyish colour and quite viscid, and has the appearance of "*sago grains*" or chloroform drops at the bottom of a urine test glass. The vesicles are believed to act as reservoirs for the spermatozoa.

Ductus Deferens.—Each ductus deferens or vas deferens is a thick-walled tube, which conducts the secretions, containing the spermatozoa, from the testis to the urethra. Each vas deferens arises from the globus minor of the epididymis, and passes up in the spermatic cord to enter the abdomen through the abdominal inguinal canal, where each separates from the other constituents of the spermatic cord. Their relations to the vesicles and bladder have already been described. The lower part of each duct is dilated and is termed the *ampulla*, the lower end of which narrows and joins the duct of the seminal vesicle to form the common ejaculatory duct, which we have seen pierces the base of the prostate and opens into the floor of the prostatic urethra at the margins of the *prostatic utricle*.

Histology.—The wall of the vas deferens is formed of an outer longitudinal layer of plain muscular tissue, surrounded by a circular layer of plain muscle tissue and an inner layer of longitudinal muscular fibres. The tube is lined with non-ciliated columnar epithelium.

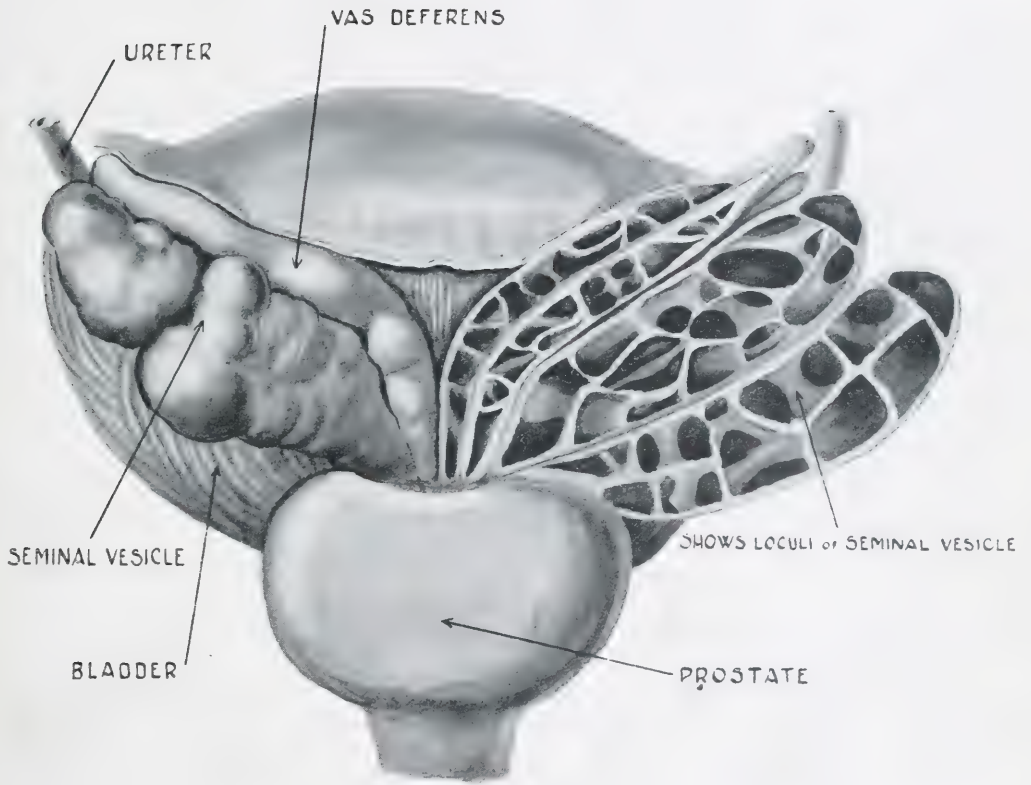
The Testis and Epididymis.—The testes lie obliquely in the scrotum, suspended by the spermatic cord, the left testis lying at a lower level than the right. Each testis is enveloped in a serous sac called the *tunica vaginalis*. Surrounding the testicle is a strong fibrous capsule called the *tunica albuginea*, this being covered externally by a layer of serous epithelium reflected from the tunica vaginalis. Fibrous processes or trabeculae pass from the inner side of the tunica albuginea to subdivide the gland of the testis into *lobules*, while posteriorly the fibrous capsule is prolonged into the interior in the form of a fibrous tissue mass called the mediastinum.

Histology of the Glandular Substance of the Testis.—The glandular substance is composed of a number of convoluted tubules (seminiferous tubules), two or more of which occupy a compartment or lobule. These fine tubules commence near the tunica albuginea, and are about two feet in length. After forming many convolutions or coils, they join up with the other tubules occupying the lobule and end in a straight tubule, which enters the mediastinum. Here it joins up with other similar straight tubules from the many other lobules of the gland, and collectively they form a complicated network of intercommunicating vessels called the *rete testis*. From the rete testis a number of efferent tubules arise called the *ductuli efferentes testis* or *vasa efferentia*, which pierce the tunica albuginea and pass into the upper extremity of the epididymis (see Pl. XII.).

The spermatozoa develop from the cells of the seminiferous tubules.

The Epididymis.—Attached to the posterior margin of the testis is an elongated mass called the epididymis. It consists of a superior extremity and an inferior extremity,

PLATE XIV



while the intervening part is called the body of the epididymis (*corpus epididymidis*). The superior extremity is globular and enlarged and is termed the *caput epididymidis* or *globus major*. This part of the epididymis is fixed to the testis by the visceral tunica vaginalis, and receives the efferent ducts from the rete testis.

The inferior extremity of the epididymis is called the *cauda epididymidis* or *globus minor*, which is also bound to the testis by the visceral tunica vaginalis, while the body of the epididymis is free and separated from the testis by an involution of the serous covering of the tunica vaginalis.

The epididymis is really a single but wonderfully coiled and convoluted tube which, if stretched out in the straight, would measure over twenty feet in length. Its upper extremity (*globus major*) receives the efferent ductules from the testis. These become coiled up to form a number of small coiled masses called the *lobuli epididymidis*, the ducts of which eventually open into a single convoluted canal to form the ultimate single coiled convoluted duct of the epididymis.

The *globus minor* is where the convoluted duct of the epididymis ends in a thick-walled muscular tube, the ductus or *vas deferens*, which, as already described, conducts the secretion to the urethra (see Pl. XII.).

Belfield (1922) contributed an interesting paper with diagrams regarding the development and comparative anatomy of the penis.

He states that the mucous lining of the vesicles consists of only one or two layers of columnar epithelial cells and is devoid of glands, lacunæ or other inaccessible pockets, unlike the urethra. For this reason he says that the entire lining of the vesicle can be medicated by fluids filling its cavity. He recommends injecting the vesicle through the *vas* with collargol, when this organ is infected with the gonococcus.

LITERATURE

BELFIELD, W. T. (1922) "Anatomy of Gonorrhœa in the Male," *Jour. Amer. Med. Assoc.*, vol. 78, p. 1290.

CHAPTER XIX

THE ANATOMY OF THE FEMALE GENITO-URINARY TRACT

By Dr. ROBERT THOMSON

The Vulva is the term applied to the external female genito-urinary tract. It includes :—

- (1) The Mons Pubis.
- (2) The Labia Majora.
- (3) The Labia Minora.
- (4) The Clitoris.
- (5) The Urethral Opening.
- (6) The Vaginal Orifice.

The Mons pubis is the prominent rounded mound covered with hair in front of the pubis.

The Labia majora are the two rounded folds of integument, which commence anteriorly at the mons pubis and extend downwards towards the anus, where they form the posterior commissure. Externally they are covered with hair, while internally they present a smooth surface, upon which are numerous sebaceous glands yielding a semi-solid sebaceous secretion.

The Labia minora lie within and under cover of the labia majora. Anteriorly they surround the clitoris, posteriorly they fade into a fold, and between this fold and the posterior border of the orifice of the vagina is the depression called the *fossa navicularis*.

The Clitoris is the homologue of the penis, and presents a glans and prepuce.

The Urethral Orifice lies about one inch below the clitoris, anterior to the vaginal orifice.

Vaginal Orifice.—In the virgin this is partially closed by the hymen, and after the hymen is ruptured its position is marked by small elevations called *carunculæ hymenales*.

The triangular area between the vagina and the clitoris is called the vestibule. The openings of Bartholin's glands lie in the groove between the vaginal orifice and the posterior part of the labia minora. These glands correspond to Cowper's glands in the male (see Pl. XV.)

The Bartholin glands were first described by Kasper Bartholin in 1677. They are oblong tubulo-racemose mucous glands situated in the lower portion of the labia majora between the superficial and middle aponeuroses. In addition to the superficial perineal fascia, their outer side is covered by the bulbo-cavernosus muscle, while the corpus cavernosus partly covers their upper portion. Their function is to lubricate the entrance to the vagina. They become atrophied after the menopause, and infection is consequently infrequent after this time. The ducts of these glands, which are about $\frac{3}{4}$ inch in length and $\frac{1}{16}$ to $\frac{1}{8}$ inch in diameter, run upward and inward to open on the inner surface of the labia minora in the sulcus between these structures and the hymen or its remains. Their orifice is but partly covered by an imperfect falciform valvular fold of mucous membrane, and they are lined with columnar epithelium.

The Female Urethra.—The canal takes a slight curved course from the neck of the bladder downwards and forwards, and opens into the vestibule, in front of the vaginal

orifice. It is about one and a half inch long. The urethra passes through the two fasciæ of the uro-genital diaphragm, between which it is surrounded by the muscle fibres of the sphincter urethræ.

The mucous membrane is thrown into longitudinal folds and is of the stratified squamous variety, except towards the bladder, where it is transitional. It contains numerous gland-follicles and lacunæ. Two long gland tubules, called the *para-urethral ducts*, or Skene's tubules, arise in the roof of the urethra, and open either directly into the urethra close to the external orifice, or directly into the vestibule near the external orifice.

Histologically the urethra consists of (1) a mucous coat ; (2) a sub-mucous coat ; and (3) a muscular coat consisting of an outer layer of circular fibres and an inner layer of longitudinal fibres.

Vagina.—The vagina is about three inches long, and is the passage which leads from the vulva to the uterus. Its anterior and posterior walls are in close apposition, and the direction of the canal is a slight curve from above downwards and forwards. It is widest at the upper end, where it is attached round the cervix of the uterus. The cavity of the upper end of the vagina, so formed by the reflection of its mucous membrane on to the cervix of the uterus, is called the fornix. The fornix is divided into an *anterior fornix*, which is in relation with the base of the bladder ; a *posterior fornix*, which extends higher than the anterior fornix, owing to the posterior wall of the vagina ascending to a higher level than the anterior wall, and is in relation to the recto-vaginal pouch of peritoneum in which lie coils of the small intestine, and part of the pelvic colon ; and on each side is a *lateral fornix*, in close relation with the ureter and uterine artery (see Pl. XVI.).

The mucous membrane of the vagina is covered with stratified squamous epithelium, and is devoid of glands, its surface being bedewed with a serous fluid, the reaction of which is acid, believed to be due to the presence of the vaginal bacillus or bacillus of Döderlein. Upon the anterior and posterior walls are two well-defined median longitudinal folds called the *columnæ rugarum*. From either side of these longitudinal folds, the mucous membrane is thrown into transverse ridges. These transverse rugose folds are especially marked in the lower part of the vaginal canal, but gradually disappear in its upper part. External to the mucous coat is a thin layer of erectile tissue, which forms an intermediate layer lying between the internal mucous coat and the external muscular coat. The external muscular coat is formed of an internal circular layer of unstripped muscle fibres and an external longitudinal layer of unstripped muscle fibres.

Uterus.—The uterus is a thick muscular hollow organ, pyriform in shape, measuring in length about three inches (75 mm.), in breadth about two inches at its broadest part, and about one inch in thickness.

Position.—Its broad upper end is directed upwards and forwards, resting upon the posterior part of the upper surface of the bladder, while its lower end is directed downwards and backwards, and is inserted into the vaginal cavity. The normal inclination of the uterus is one of antelexion—the axis of the uterus forming a right angle with the axis of the vagina. The uterus is suspended within the pelvis by means of the broad ligament, which consists of two folds of peritoneum, which stretch from the lateral walls of the uterus to the side walls of the pelvis.

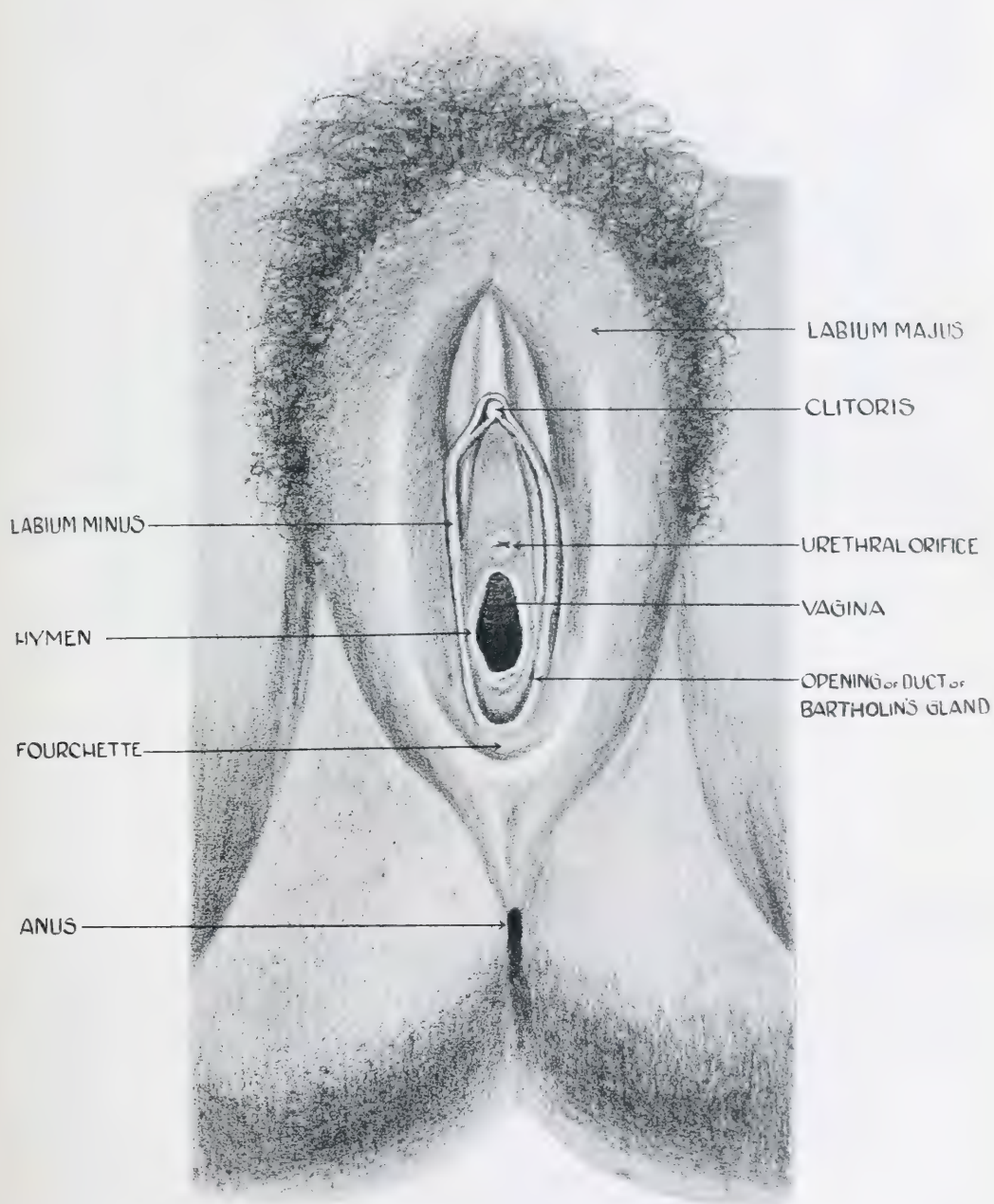
The uterus consists of a fundus, a body, and a cervix.

The fundus is the rounded upper end of the uterus represented by a line above the points where the Fallopian tubes enter.

The body is the intervening part between the fundus and neck of the uterus or cervix.

The cervix or neck of the uterus is about one inch in length (25 mm.) ; it is almost cylindrical in shape, and projects into the upper end of the vagina. The orifice of the cervix which opens into the vagina is called *os uteri externum*. This opening in the nullipara is a transverse slit, with rounded anterior and posterior lips, but in multiparae the orifice is larger, and irregular or stellate in shape. The orifice which leads from the cervix to the body of the uterus is called *os uteri internum*.

PLATE XV



Ligaments of the Uterus — *Ligamenta lata uteri* (broad ligaments of the uterus).—These stretch from the lateral borders of the uterus to the side walls of the pelvis, and thus suspend the uterus within the pelvis. The upper part or superior border of each broad ligament contains the Fallopian tube, while the part of the superior border which extends beyond the tube contains the ovarian vessels and nerves, and forms the *suspensory ligament of the ovary*. The lower or inferior border rests medially on the upper end of the vagina, while laterally it rests on the levator ani muscle. Two small secondary folds arise from the broad ligament, viz. one from the anterior surface and one from the posterior surface. The one from the anterior surface is called the *ligamentum teres uteri* (*round ligament*), and consists of two cord-like bands, one on either side. They are composed of involuntary muscle fibres and connective tissue. These round ligaments are attached to the body of the uterus, just below the entrance of the Fallopian tubes, and pass forwards and laterally, between the layers of the broad ligament, to the side walls of the pelvis, and each finally ends by passing through the abdominal inguinal ring into the inguinal canal.

The one from the posterior surface of the broad ligament stretches from the fundus of the uterus, below the entrance of the Fallopian tube, and passes out to contain the ovary. The part of this fold, which stretches from the fundus of the uterus to the lower pole of the ovary, forms a cord-like ligament, and is called the *ligament of the ovary*.

Structure of the Uterus.—The mucous membrane of the body of the uterus differs from that of the cervix. In the body it is smooth, very thick, and composed of soft connective tissue, containing a large number of spindle-shaped cells. It contains long simple tubular glands, which take a convoluted course in passing through the mucous membrane. They are lined with ciliated epithelium continuous with the epithelium covering the inner surface of the mucous membrane of the body. The mucous membrane is very vascular, and contains large numbers of lymphatics.

The *mucous membrane of the cervix*, on the other hand, is marked by longitudinal and oblique ridges, this arrangement being termed from its appearance the *arbor vitæ*. The glands are shorter than in the body.

The secretion of the uterus is slightly alkaline in reaction, and contains mucus secreted from the cervical and uterine glands.

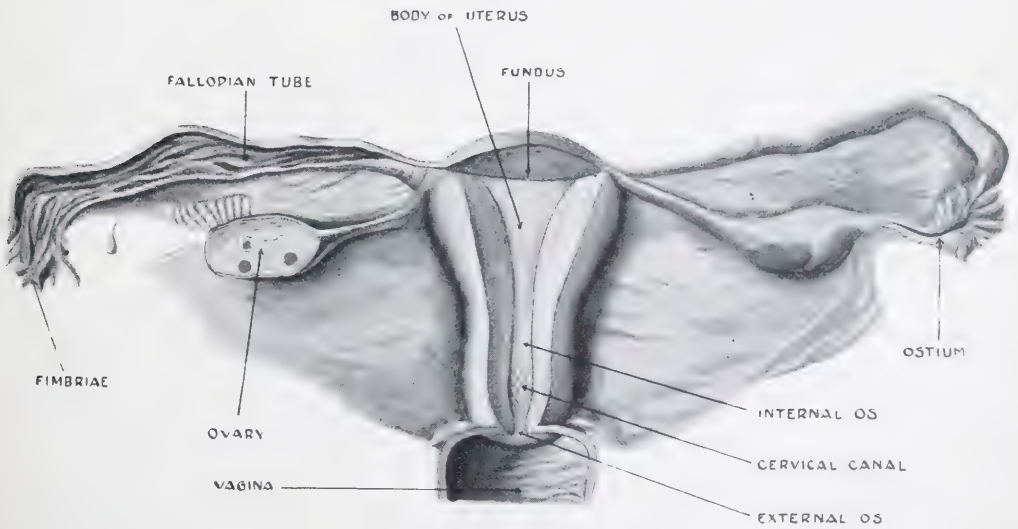
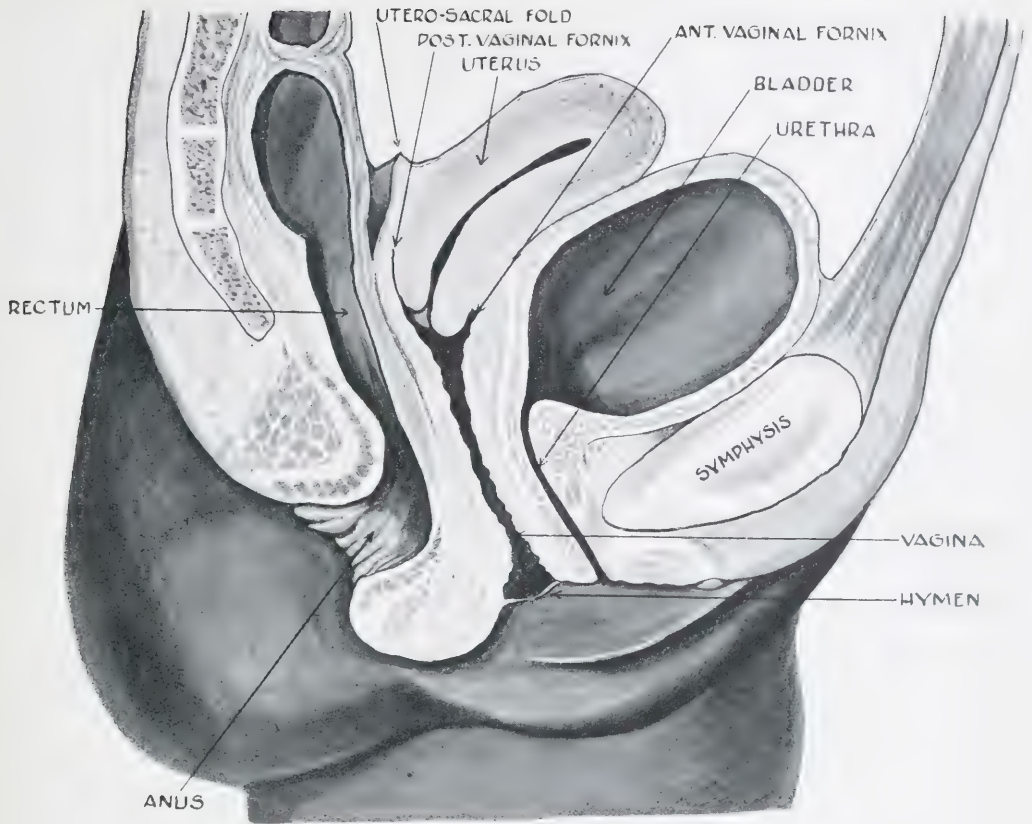
External to the mucous membrane is a thick muscular layer formed of plain or unstripped muscular fibres disposed in two strata, viz. an inner layer arranged circularly, and an outer layer arranged longitudinally. The inner layer is much the thicker, and contains the terminations of the uterine tubular glands, between and among its fibres.

External to the muscular coat is a serous layer derived from the peritoneum, which covers the greater part of the fundus.

Fallopian Tubes (*Tubæ uterinæ*).—Each Fallopian tube is about four inches long, and is contained in the upper border of the broad ligament. Each tube opens into the uterus at the junction of the fundus and body of the uterus, while as it passes outwards to the side wall of the pelvis it curls round towards the upper pole of the ovary, pierces the broad ligament, and communicates with the peritoneal cavity by a very narrow orifice called the *ostium abdominale*, where it terminates in a number of fringe-like processes called the *fimbriæ*. By one of these fimbriæ, viz. the fimbria ovarica, it is attached to the upper pole of the ovary. Tracing the Fallopian tube from the uterus, the calibre of the canal for a short distance is very fine, and will only admit a fine bristle; this portion is called the *isthmus tubæ uterinæ*: as the tube extends laterally, however, it becomes slightly dilated and convoluted, and this part is called the *ampulla tubæ uterinæ*; finally the tube terminates in the fimbriæ, which, collectively, constitute the infundibulum tubæ uterinæ.

The *mucosa* of the tube is thrown into a series of longitudinal folds and is lined with ciliated epithelium, the movement of the cilia being directed towards the uterus. External to the mucous membrane is a muscular coat, consisting of an internal circular layer and an external longitudinal layer of unstripped muscle fibres. External to the muscular layer is a serous coat of peritoneum formed by the layers of the broad ligament.

PLATE XVI



The function of the Fallopian tube is to convey the ova from the ovaries to the uterus.

Impregnation of the ova, by the spermatozoa, in most cases takes place in the tubes.

The Ovary (*Ovarium*).—The ovaries are two small flattened ovoid glandular bodies about the size of a pigeon's egg. The long axis of each ovary is vertical, its upper pole being in close relation to the infundibulum of the Fallopian tube. Each ovary lies in a recess in the side wall of the pelvis called the fossa ovarica, and is attached to the posterior surface of the broad ligament by a secondary fold of the posterior layer of the ligament, called the *mesovarium*, while its lower pole is connected with the uterus by a cord-like ligament, viz. the ligament of the ovary, which is attached to the uterus, immediately below and posterior to the entrance of the Fallopian tube (see Pl. XVI.).

CHAPTER XX

THE MORBID HISTOLOGY OF GONORRHOËAL AFFECTIONS OF THE GENITAL MUCOUS MEMBRANE

COMPARATIVE SUSCEPTIBILITY OF COLUMNAR AND SQUAMOUS EPITHELIUM—NORMAL URETHRA—CHANGES IN THE EPITHELIUM DUE TO GONORRHOËA—THE URETHRAL GLANDS—PROSTATE—VESICLES—EPIDIDYMIS—URETHRAL POLYPI—BARTHOLIN'S GLANDS—SALPINGITIS

THE researches by various workers on the histological changes which occur in the mucous membrane as a result of gonorrhœal inflammation are on the whole very complete.

Bumm (1885) was the first to carry out such investigations, and we are indebted to him more especially for his researches on the changes which occur in the conjunctival tissues as a result of gonorrhœal ophthalmia. With regard to the urethra, it may be said that the histology has been studied from the commencement of the gonococcal infection up to the remotest lesions which it produces.

According to Luys (1917) histological and urethroscopical researches complete each other, and should go hand in hand. The pathological changes in chronic urethritis are clearly visible during life, but they become invisible to the naked eye after death, because the local congestion and œdema vanish with the cessation of life. These changes only become apparent through microscopic examination of sections of the diseased tissues.

Finger inoculated moribund patients with gonorrhœa, and was then able to make detailed examinations of the urethra thirty-six to forty-eight hours after the commencement of the infection. We are indebted to him, therefore, for our knowledge of the changes produced by the disease in its earliest beginnings.

Dinkler (1892) and Councilman studied the conditions which occur later on in urethritis, whilst Jadassohn (1890), Touton (1892–1893), and Pick (1907) worked out the histological changes which occur in the para-urethral and preputial ducts and glands.

Amongst the other authors who have studied the morbid histology of gonorrhœa, the important works of Oberländer and Neelsen, Oberländer and Kollmann (1910), Baraban, Wassermann and Hallé, Fabry, Wossidlo (1903), and Motz (1903) should be mentioned. These investigations supplement each other, and give a complete insight into the activity of the gonococcus within the urethral mucous membrane.

Finally, we must mention the researches by Wertheim (1891–92), Schridde (1908), and others on gonorrhœal affections of the uterus and its appendages, viz. the tubes and ovaries.

In gonorrhœal infections of the mucous membranes the gonococci multiply rapidly, and spread at first over the surface of the epithelial cells. The germs, however, very quickly penetrate, and multiply more deeply in the spaces between the cells.

According to Bumm and Finger they soon find their way into the superficial layers of the submucous tissues. Of course, it must be remembered that Finger was dealing only with very weak and moribund subjects, and it is possible that the penetrating power of the germ might not be quite so great in the case of young and vigorous subjects.

Comparative Susceptibility of Columnar and Squamous Epithelium.—It was at first believed that the gonococcus could only attack the mucous membranes which were lined with cylindrical epithelium such as that of the urethra. The researches of Jadassohn, Touton, and Dinkler proved, however, that pavement epithelium could also be attacked. Jadassohn nevertheless noted that different mucous membranes varied in susceptibility, and it is now generally accepted that the cylindrical epithelium is certainly much more easily infected than the squamous type.

Jadassohn observed that in the case of mucous membranes lined with cylindrical epithelium the gonococci penetrated readily into the submucous connective tissues. When, however, the surface consists of pavement epithelium, this deep penetration of the germ is seldom seen. This peculiarity was also noted by Finger.

According to Luys (1917) it is a matter of common knowledge that the gonococcus penetrates into a normal urethra which has never been infected, and has a healthy cylindrical epithelium, much more easily and readily than into one which has been infected some time or other. This fact explains why abortive treatment by means of immediate irrigations is much more often a failure in fresh cases than in subsequent attacks. One of the consequences of gonorrheal infection of the urethra is destruction of the cylindrical epithelium and its replacement by pavement epithelium. After a couple of attacks the urethra has undergone such modifications as to become a bad soil for the gonococcus. The organism finds it difficult to penetrate into the epithelium, and thus the chances of a well-conducted abortive treatment proving successful are infinitely greater.

Invasion of the Normal Urethra by the Gonococcus.—When the gonococcus gains access to the healthy urethra it finds the soil favourable and commences to multiply. For the first thirty-six hours or thereabouts the germs remain on the surface, and this period, which is free from symptoms, is termed the *incubation period*. As soon, however, as the gonococci commence to multiply between the cells and penetrate into the deeper tissues, the toxicity of the organism brings about a severe inflammatory reaction. Serum is poured out into the tissues and large numbers of polynuclear neutrophile leucocytes migrate into the inflamed area. These leucocytes or pus cells penetrate between the epithelial cells, and accumulate as pus in the lumen of the urethra. Simultaneously the superficial layers of the submucosal tissues become markedly infiltrated with polynuclear and mononuclear leucocytes and with plasma cells.

By the multiplication of the gonococci in the inter-epithelial interstices the connections of the epithelial cells become loosened. This is further accentuated by the exudation of serum, and more especially by the enormous emigration of white blood corpuscles. In consequence the epithelial cells become separated, and in many places completely lifted away from their basement membrane.

This intense inflammatory reaction of the tissues, which usually begins about the third day, is an attempt on the part of the body to defend itself against the invasion of a pathogenic irritant. The leucocytes and serum are brought to the scene of attack by the dilated capillaries. A struggle then takes place within the mucosa between the germs and the white corpuscles, and the latter, after engulfing large numbers of gonococci, apparently succumb. These dead leucocytes along with their load of germs are discharged into the lumen of the urethra, thus giving rise to a flow of pus from the meatus.

If microscopic sections are prepared from a urethra at this stage of the disease it will be noted that wherever gonococci are found, there also large numbers of polynuclear leucocytes are present. Even in the connective-tissue layers one finds these pus cells containing the germs. Generally, however, in the deeper parts of the tissues the gonococci are more commonly extra-cellular than intra-cellular, which is the opposite to what one finds on the surface. As a rule the sections show that the lymphocytes, eosinophiles, and mast cells do not ingest the cocci. Further, the connective-tissue and plasma cells are also free from them. It is markedly noticeable that the storage of gonococci within the polynuclear leucocytes is most pronounced in the superficial layers of the mucous

membrane and in the lumen of the urethra. Jadassohn describes shortly this characteristic difference in the tissues and in the lumen as follows: "*In the latter many intra-cellular, in the former many extra-cellular gonococci.*"

The gonococci do not enter into the epithelial cells, but, as already stated, penetrate and multiply between them. In sections they can be seen lying in longer or shorter rows in the inter-epithelial interstices. Wherever these interstices are dilated with serous exudate the germs occur in spherical colonies. The gonococci very seldom penetrate into the capillary blood-vessels. Sometimes, however, according to Bumm, they extend from the surface into the deeper tissues in perpendicular chains, and it is even possible to find them penetrating in this manner into the capillary lymph spaces.

Quite early in the course of gonorrhoeal inflammation the mucosa becomes charged with embryonic cells. These are found in some cases in the superficial layers only. In other cases they occur throughout the entire thickness of the mucosa, no doubt due to the fact that in them the gonococcus has penetrated more deeply. Where the whole



FIG. 6.—Normal urethra, penile portion. Low power.



FIG. 7.—Normal urethra. High-power magnification.

mucosa is affected in this manner it becomes, according to Luys, thickened, roughened, and inelastic, and bleeds readily. Again, the inflammation may spread still further to the sub-epithelial connective tissue, and even to the trabeculae of the corpora cavernosa. These in consequence are swollen and infiltrated with embryonic cells, serous exudate, and leucocytes. Phlebitis may supervene as a result, as well as endo- and peri-arteritis. The lymphatics may also be involved, accompanied by painful enlargement of the lymphatic glands, which may even suppurate.

Changes in the Epithelium due to Gonorrhoea.—When the inflammation has passed its maximum intensity and the tissues appear to have gained the upper hand, an attempt is made to repair the damage which has been done. A marked proliferation of embryonic cells occurs, and in place of the original single layer of surface cylindrical epithelium there is developed a coating which consists of several tiers of cells, and in which the cylindrical variety reverts to a more cubical or even squamous type. This change in the epithelial surface-lining, which was first described by Finger, is very well illustrated in the accompanying diagrams reproduced from Motz's work on the subject (1903).

Fig. 8 shows the condition of the urethral mucous membrane in the very earliest

stages of gonorrhœa, where the cylindrical epithelium is almost normal but there is a considerable infiltration of round cells (polynuclear leucocytes).



FIG. 8.—Superficial infiltration of urethra. Cylindrical epithelium almost normal.

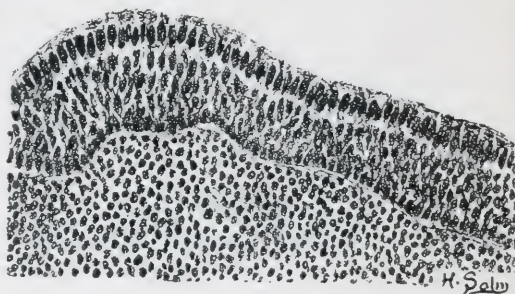


FIG. 9.—Superficial urethral infiltration. The cylindrical epithelium is proliferated.

Fig. 9 shows a later stage in which the cylindrical epithelium has become greatly proliferated in the attempt to repair the damage. This process of repair is well marked about the fifth or sixth week.



FIG. 10.—Superficial infiltration of urethra. Stratified cylindrical epithelium covered with a layer of pavement epithelium.

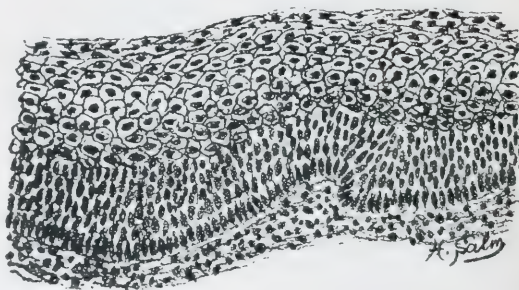


FIG. 11.—Superficial infiltration of urethra. Epithelium largely composed of many layers of pavement and cylindrical epithelium.

Fig. 10 shows the commencement of stratification of the new proliferated epithelium, which never reassumes the cylindrical type. The stratification begins on the surface and extends downwards.

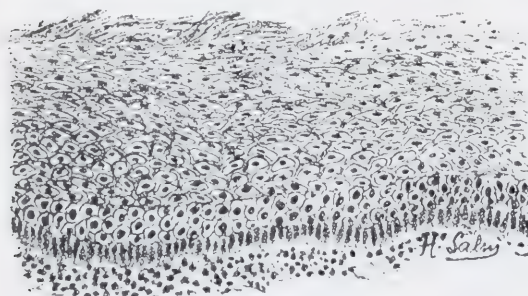


FIG. 12.—Superficial infiltration of urethra. The epithelium is keratinised.

Fig. 11 shows a still later stage in the process of stratification. The new epithelial lining may show as many as seven or eight layers, and forms a tough skin, which is less supple and more impermeable to antiseptics than the original single layer of cylindrical epithelium.

Fig. 12 shows the final stage in the evolution of the new epithelium which occurs in chronic urethritis. The layers of cells become still more flattened and eventually keratinised, so that the surface becomes more like skin than a mucous

membrane, hence its impermeability to antiseptics.

Motz states " that most chronic infiltrations are protected by a thick shell which is almost impermeable to chemicals. This is the true reason why it is so difficult to disinfect

these superficial infiltrations, which sometimes last twenty or thirty years, as the autopsies on patients who have died from strictures show."

Changes in the Urethral Glands due to Gonorrhœa.—If the attack of gonorrhœa has been mild, or of short duration, the whole of the injured surface may be rapidly repaired, and no further trouble results. As a rule, however, it is only repaired in places, whilst in other portions the germs continue to survive, and the inflammation continues in a more or less chronic form. The persistence of uncured patches in which gonococci survive, and where in consequence the healing process is delayed, is due to the presence of infected glands. It has been amply proved that the gonococci can penetrate through the excretory ducts of the Littre's follicles and other glands, and thereby the same inflammatory processes are produced in these diverticula as on the surface of the urethra itself.

Unfortunately, antiseptic irrigations seldom or never penetrate into infected follicles. In fact, the glands with their excretory ducts are sites of refuge wherein the gonococcus can survive in a more or less latent condition for an extraordinarily long period of time.

Jadassohn pointed out that the excretory ducts of the follicles were very liable to become blocked. In consequence the inflammatory exudate is unable to discharge, with the resulting formation of retention cysts.

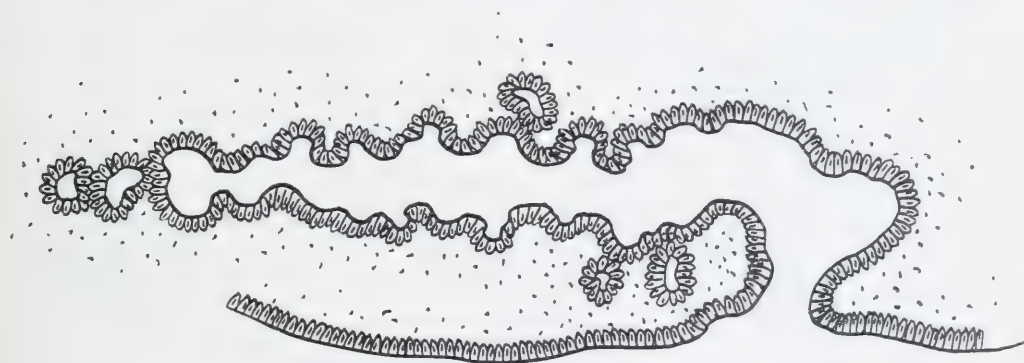


FIG. 13.—Diagrammatic section of a normal Littre's gland. (D. Thomson.)

When the glands become infected with the gonococcus, other organisms follow in their trail. These secondary organisms consist of staphylococci, pneumococci, diphtheroids, strepto-pneumococci, *B. coli*, etc. Sometimes the gonococcus dies out but the secondary infection remains and is capable of keeping up a more or less mild chronic inflammation resulting in a morning drop and shreds in the urine.

If the gonorrhœal infection stops in front of the membranous sphincter we speak of an *anterior urethritis*; if it passes beyond that muscle a *posterior urethritis* is present. According to Finger and Jadassohn, the posterior urethra becomes involved in 60 per cent to 70 per cent of all cases. A posterior urethritis is always more serious, owing to the possibility of complications arising, such as prostatitis, vesiculitis, Cowperitis, pyelonephritis, etc.

What has been said with regard to the morbid histology of the male is also true in the case of the female.

The glands of Bartholin, Skene's ducts, the cervical and uterine glands, etc., become infected in the same manner, and the same histological changes take place. Jadassohn stated that the Bartholin glands were especially liable to become secondarily infected with anaerobic bacteria. The ducts are apt to become occluded, due to the thickening of their walls and the serous exudation. When this occurs the purulent material is unable to drain away, so that sometimes the result is abscess formation and sloughing. The cause of the occlusion of the gland ducts is very easily understood from the following diagrams by Motz (1903).

Figs. 14 to 18 show various stages in the inflammatory process which occurs in the urethral glands.



FIG. 14.—Chronic urethritis. Epithelium almost normal; superficial and deep infiltrations. Urethral adenitis; inflammation of glands.

The infected Littre's follicles and lacunæ of Morgagni become swollen, and their openings form crater-like orifices. Infiltration and proliferation of cells occurs, as shown in the diagrams, and the lumen becomes obstructed and filled with pus and cellular debris. The walls of the ducts and orifices become so swollen and infiltrated that the lumen is obliterated. In consequence the swollen glands become converted into cysts which appear on the surface of the mucous membrane as whitish nodules. Less often they suppurate, and give rise to periurethral abscesses and fistulæ.

When the inflammation has more or less died down the marked proliferation of tissue begins to be absorbed. It becomes drier and less turgid, and shrinks to its normal size. Most commonly, however, the embryonic cells, instead of being completely absorbed, degenerate into fibrous tissue, which gradually shrinks and strangulates the glandular epithelium. In consequence the gland itself becomes obliterated and its place is taken by a tiny fibrous nodule.

The urethral glands play an important rôle in gonorrhoeal inflammations, because they are largely responsible for the unfortunate tenacity and chronicity of the disease. As already stated, the gonococci find shelter from the antiseptic irrigations within these glandular culs-de-sac; and even where the greater portion of the mucosal surface of the urethra has again become normal, the glandular infection remains, and may result in a recrudescence of the disease by reinfesting the whole mucous surface of the urethra over again.

In very chronic gonorrhoea as a rule we find that the urethral surface on the whole is healed up and covered with keratinised flattened epithelium. At certain patches, however, the inflammation remains on account of the infected Littre's glands. Eventually these Littre's follicles may be obliterated and

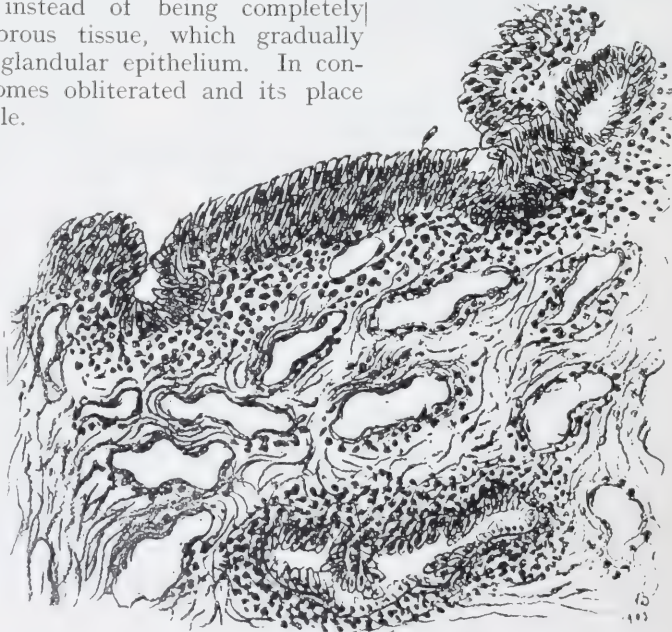


FIG. 15.—Chronic urethritis. Stratified cylindrical epithelium; superficial embryonic infiltration. Adenitis.

become small fibrous nodules, as described above. The contracting fibrous tissue is one of Nature's methods of obliterating the last traces of an inflammatory focus. Unfortunately, however, this healing process is liable to cause stricture-formation. When a zone of inflammatory tissue around the lumen of the urethra begins to degenerate into fibrous tissue, the gradual shrinkage of the latter leads to an annular stricture. The formation of these strictures, however, is sometimes more deeply laid. In gonorrhœa the peri-urethral tissue and the corpora cavernosa may be invaded by the same changes as the mucous membrane, viz. round-celled infiltration, proliferation of embryonic cells (repair), followed later by absorption and degeneration into fibrous tissue, with the formation of hard retracted bands. Strictures are very common in the posterior membranous portion of the urethra. This is due to the fact that the inflamed mucosa in this portion of the urethra is more easily fissured and split, either by instrumental interference, or due alone to the contraction of the sphincter muscle. Thus more or less deep rhagades are formed, which bleed easily.

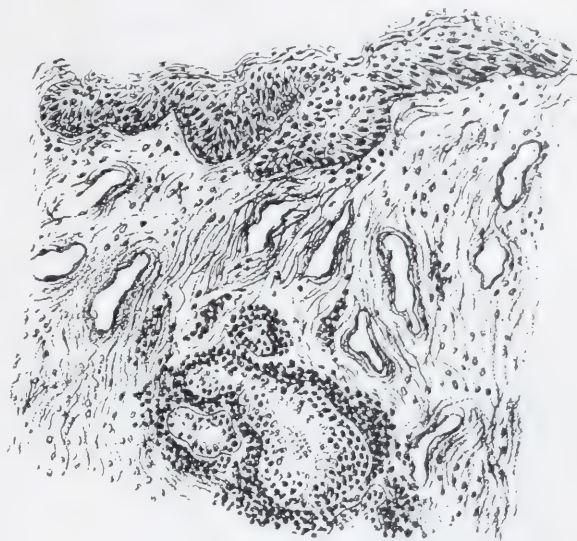


FIG. 16.—Chronic glandular urethritis. Stratified cylindrical epithelium covered by several layers of pavement epithelium. Mucosa and submucosa cured. Adenitis.



FIG. 17.—Chronic superficial and deep urethritis. Epithelium keratinised; superficial embryonic infiltrations. Urethral adenitis.

When the inflammation dies down the fissures leave fibrous scars, which gradually contract and tend to narrow the lumen of the pipe.

Further back in the prostatic urethra, gonococcal inflammation causes a distortion of the mucous membrane, and the fibrous tissue which is eventually formed is liable to compress and even obliterate the orifices of the ejaculatory ducts. If these ducts themselves have been affected, the same fibrous strangulation is liable to occur eventually in the ducts themselves. Sometimes only the orifice of an ejaculatory duct is involved, and in cases of this kind the opening becomes sclerosed and narrowed. This is supposed

to account for the shooting pain felt by certain patients during ejaculation, when the semen is in the act of passing the narrowed orifice. Again, as the result of fibrosis the

more or less rigid ejaculatory ducts may not be able to shut off the seminal vesicles completely, and so they allow the semen to percolate through all the time. This condition of spermatorrhœa is not uncommon as a result of chronic gonorrhœa.

Infection of the Prostate.—The prostatic glandules are very frequently attacked by the gonococcus, and undergo the same process of congestion, infiltration, proliferation, and fibrosis. The inflammation may be muco-purulent or purulent. In the first case the prostatic discharge is whitish in colour, and consists of an excessive amount of mucous or desquamated epithelial cells. In the second case the discharge is thick and yellowish, and consists largely of polymorphonuclear cells.

In the more severe cases necrosis and destruction of the glandular substance occurs; *vide* De Keersmaecker and Verhoogen (1898). As in the case of the urethra, the last stage of the inflammatory process is a certain amount of fibrosis. The fibrous tissue contracts and thereby may strangulate and destroy the gland substance. The prostate in consequence becomes hard and nodular.

The gonococcal infection may eventually die out, but very often the germs lie latent in the more or less fibrosed tissue. In this situation it is very difficult to eradicate them either by chemical or vaccine treatment. The chemicals are unable to penetrate, and even anti-substances in the blood stream are unable to reach them on account of the scanty blood supply to the part.

Infection of the Vesicles.—These organs are very vascular, and when congested by gonococcal inflammation they are very likely to bleed, so that a brownish granular sediment appears in the urine. In the last stages the vesicles become fibrosed, distorted, and hardened.

Infection of the Epididymis.—The glandular and tubular substance, at first congested, swollen, and turgid, ends in fibrosis, strangulation, and destruction.

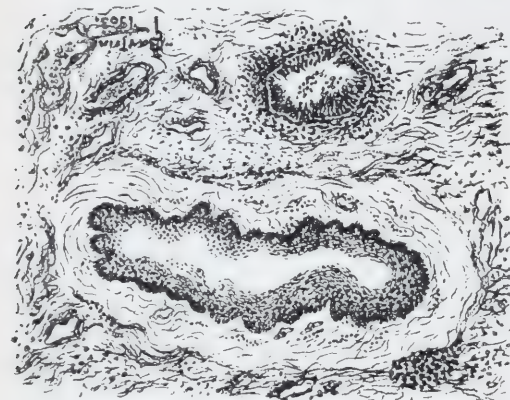


FIG. 18.—Deep chronic urethritis. Keratinised epithelium. Sclerosis of mucosa and submucosa. Deep infiltration. Adenitis.

Very often a hard fibrous nodule is left after the disease has died down. The very acute cases may go on to suppuration. In practically all severe cases of epididymitis the tubules are occluded by the fibrosis, and the gland substance is strangulated and destroyed. In cases of double epididymitis this process results in complete sterility.

Urethral Polypi.—According to Luys (1917), gonorrhœa may result in the formation of urethral polypi; *vide* Oberländer (1893), Grégoire (1904), Burckhardt (1906), and Pelletier (1911). The condition may follow immediately after the acute stage of the gonococcal inflammation, as a result of hypertrophy of the papillæ, or it may arise at a later period, subsequent to the formation of strictures.

According to Burckhardt there are four varieties of gonorrhœal polypi:—

(1) *Caruncles.*—These are small raspberry-like vascular tumours with a more or less well-defined pedicle. They occur most commonly in women, and are usually situated around the urinary meatus. They bleed readily on account of their vascularity. Histologically they are composed mainly of numerous dilated blood-vessels covered by a pavement epithelium of moderate thickness.

(2) *Papillomata.*—These can be recognised by the naked eye. The papillæ consist of a core or stroma with blood-vessels. They are lined with a thick layer of pavement epithelium.

(3) *Condylomata.*—These have the naked-eye appearance of little cock's-combs.

As in the case of papillomata, they consist of a thick layer of epithelium over a compact core of stroma. The latter, however, is comparatively poor in blood-vessels.

(4) *Glandular and Mucous Polyypi*.—These are adenomatous in nature, and appear to arise from a hypertrophy or hyperplasia of the glands of the mucous membrane. They are composed of a stroma of loose tissue containing numerous glands, and the whole growth is covered with several layers of epithelial cells.

Uteau and Saint-Martin (1913) state that the persistence of chronic gonorrhœa is sometimes explained by the presence of polyypi in the urethra.

Bartholin's Glands.—Stevens and Heppner (1920) examined 3439 prostitutes and found by smears and the complement-fixation test that 1496, or approximately 43·5 per cent., had a chronic gonorrhœal infection. Of the infected cases they found the cervix involved in 47 per cent, the urethra in 32 per cent, and the Bartholin glands in 23 per cent. The ducts of Bartholin's glands are lined with columnar epithelium, which is a favourite habitat of the gonococcus. Because of their position, the liability of these glands and their ducts to both primary and secondary infection is also increased. In addition to gonococci, other diplococci, streptococci, and staphylococci are often found. Occlusion of the ducts is frequent, and results in the formation of an abscess or cyst, depending on the presence or absence of an infection in the gland. Strictures of the duct are also common. A filiform bougie is of more value than the probe in the diagnosis of both conditions. Although it is usually impossible to palpate a normal Bartholin's gland, an infected gland can be detected in the majority of instances. A palpable gland is usually infected; consequently, according to these authors, its removal is advisable, even although gonococci cannot be found in it. Occlusion of the duct may be but temporary, and is not a contra-indication to this procedure. They found injections of acriflavine, mercurio-chrome, etc., to be of little value in eradicating the infection from these glands.

Salpingitis.—The presence of plasma cells in an abscess of the Fallopian tubes has been stated by Schridde (1910) to be diagnostic of gonococcal salpingitis, but Miller (1912) also found these plasma cells in cases of salpingitis of different origin, notably in tubercular salpingitis. Schridde further states that in gonococcal pyosalpinx there is superficial ulceration of the mucous membrane, and lymphocytes are found amongst the pus cells.

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CHAPTER XXI

THE CYTOLOGY OF GONORRHOEAL DISCHARGES

SEVERAL papers have been written on this subject by various authors in the past.

According to Man and Polano (1905), the number of mono-nucleated cells in the discharge increases with the age of the disease, and they indicate a process of regeneration in the submucosa. They also state that *eosinophile leucocytes* occur later in the disease, from about the fourth to the sixth week, and mast cells were noted in 30 out of 200 cases.

Osner (1906) found that he was unable to diagnose the duration of the disease by microscopic examination, because he found that the polymorphonuclear and mono-nucleated cells occurred in all stages. He admits, however, that the mononucleated variety is more commonly found in the very early and in the very late stages of the disease.

Isolated eosinophile leucocytes were observed in all stages, but were more often found about the fifth or sixth week. He maintained that the so-called round nuclear or ball-nucleated cells were an indication of a peculiar degeneration, and were found chiefly in old chronic cases of about one year's duration. These cells were found in 57 out of 227 preparations, and he believed that they marked the presence of a secondary or mixed infection.

Taylor (1907) failed to find anything of value from the cytological study of the gonorrhoeal discharges.

He states that the remarks made by different authors on the significance and the presence of eosinophiles are very discordant.

Regarding the lymphocytes, Pappenheim believed that they indicated the stages of repair, but they are found all through the disease, as pointed out by Neuberger (1906). Ball-nucleated leucocytes, in which the nucleus appears as three or four balls not connected with one another, are found in non-gonorrhoeal as well as gonococcal urethritis, and so they have no diagnostic significance.

Von Stabsarzt and Kutscher (1909) state that in the very earliest stage of gonorrhoea the discharge is mostly mucus, with a few epithelial cells. The gonococci are then usually lying free, or are plastered over the surface of the epithelial cells. During the middle stage of the disease pus cells (polymorphonuclear leucocytes) are very numerous; whilst in the last stage there is a preponderance of epithelium and few pus cells.

In isolated cases the observers found that the gonococci were extra-cellular almost exclusively throughout the whole course of the illness.

According to Jadassohn (1910) the discharge in the early stage of gonorrhoea is serous; later it becomes definitely purulent. In the last stage it becomes more muco-purulent, and there may be a certain amount of desquamative catarrh. Exceptional cases occur in which the discharge is fibrinous and the mucous membrane has a diphtheritic appearance. This condition may be intense enough sometimes to be hæmorrhagic.

The epithelial cells which are found in the urethral discharge often show the keratin granules of Ernst. These granules, which are Gram-positive, are, according to Ernst, an indication of the earliest stages of keratinisation of the epithelium.

Jadassohn quotes Neisser as the first observer to find a connection between the occurrence of eosinophiles and the involvement of the Littre's glands, and especially of the prostate. Others, however, have failed to find any such connection.

Gassmann observed numerous eosinophiles in the discharge in two cases, shortly after the occurrence of epididymitis.

Pezzoli found eosinophiles in cases of anterior urethritis, but considered that they were perhaps less numerous than in those cases where the posterior urethra is affected, and they occurred most frequently in chronic gonorrhœa when the prostate was involved. In his opinion the secretions from the Littre's glands were generally poor in eosinophiles. They were relatively more often found in the secretions of Bartholin's glands, and in para-urethral and peri-urethral abscesses.

As a rule the eosinophiles were scarcer in the gonorrhœal discharge in the female than in the male.

They were commonly found, however, in the vulvo-vaginitis of little girls.

Muir and Ritchie (1913) state that in the earliest stage of gonorrhœa, when the secretion is glairy, a considerable number of the gonococci are lying free or adhering to the surface of the desquamated epithelial cells, but when it becomes purulent, the large proportion within the leucocytes is a very striking feature.

Further articles on this subject have been written by Steele (1914) and Cedercreutz (1915).

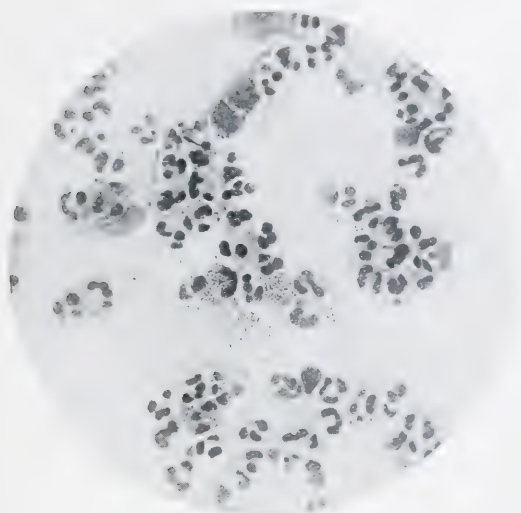
Ramond and Charlet (1917) took the blood count and the gonococcus count systematically in 9 cases of acute gonorrhœa, examining 127 specimens of the gonorrhœal pus. They could not detect any regularity or any bearing on the prognosis from either the blood or gonococcus count. One finding, however, was suggestive, viz. the constancy of the acme of the curve of the total gonococci in the course of the third week. This they say suggests a partial immunisation of the body to the gonorrhœal infection localised in the urethra.

The Author's Observations.—The writer does not feel competent to say much on the cytology of the discharges in the different stages of gonorrhœa, since he has always stained the smears by Gram's method. By this method eosinophile granules and other cytological characteristics are not well depicted. It may be accepted on the whole, however, that in the acute and subacute stages of the disease the discharge is chiefly purulent, and consists largely of polymorphonuclear cells, whereas in the chronic stages, and especially in old gleans, the discharge is more whitish, and consists of a large proportion of epithelial and mononucleated cells (see Pl. XVII., Nos. 1 and 2). The peculiar stippling of the epithelial cells with minute Gram-positive granules has often been noted. Whether or not these indicate the early stage of the keratinisation as claimed by Ernst, the author is not prepared to state. At any rate he has also noted this stippling in the epithelial cells obtained from the skin in cases of gonococcal keratoderma. In urethral discharges it was found that the epithelial cells which were infected with diphtheroid organisms were almost invariably stippled. Dr. J. Gordon Thomson (unpublished observations) maintains that, when acting as pathologist to a large army venereal camp in Egypt, he was able to detect, by microscopic examination of the discharge, those cases of gonorrhœa which were developing stricture formation. He maintains that the occurrence of stricture is accompanied by the presence of fibroblasts in the discharges. The author is unable to state whether any observations on this matter have been made by others.

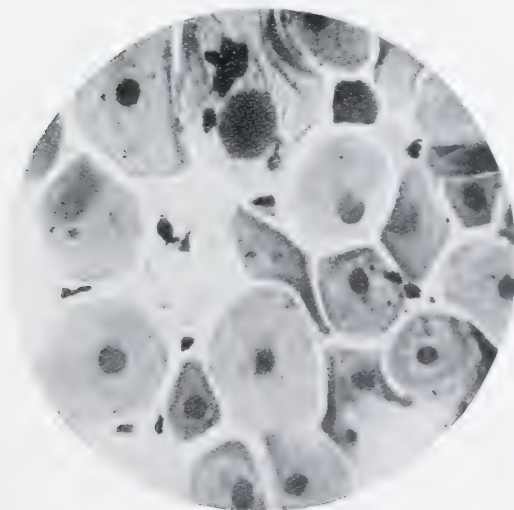
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PLATE XVII



No. 1 shows the typical cytology of the discharge in a case of acute gonorrhœa. The material consists chiefly of polymorphonuclear leucocytes (pus cells). Magnification 500 diameters.



No. 2 is the type of discharge often found in cases of chronic gleet. The material is whitish, and consists chiefly of flat epithelial cells, with an occasional pus cell. Magnification 500 diameters.

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CHAPTER XXII

THE PARTS OF THE BODY SUSCEPTIBLE TO DIRECT INFECTION WITH THE GONOCOCCUS

URETHRA — VULVA — VAGINA — LITTRITIS — FOLLICULITIS — COWPERITIS — PROSTATIS —
VESICULITIS—EPIDIDYMITIS—CYSTITIS—PYELITIS AND PYELO-NEPHRITIS—PROCTITIS—
GONORRHŒA, ORAL AND NASAL—GONORRHŒAL INFECTION OF THE EAR—DIRECT SKIN
INFECTIONS — CONJUNCTIVITIS — FEMALE INFECTIONS: URETHRITIS, VAGINITIS, CER-
VICITIS, METRITIS, ENDOMETRITIS, SALPINGITIS, OVARITIS, PERITONITIS—BARTHOINITIS
—VULVO-VAGINITIS OF INFANTS—GONORRHŒA IN LITTLE BOYS

Urethra, Vulva, and Vagina.—The moist mucous membrane of the genital tract is the true home of the gonococcus. The urethral mucosa of both sexes is extraordinarily liable to infection. Next in order of susceptibility is the conjunctival mucous membrane in childhood. Strangely enough, with increasing age this susceptibility decreases, so that in adults, in spite of the numerous opportunities for infection, gonorrhœal ophthalmia is comparatively rare.

In the adult male the infection begins typically in the mucous membrane of the anterior urethra, and may spread to the posterior urethra, the prostate, the vesicles, the epididymis, and the bladder.

In the female the infection is usually more complicated, since it attacks not only the urethra and bladder, but also the vulva, vagina, Bartholin's ducts and glands, also the cervical canal, and very often spreads to the endometrium and to the Fallopian tubes. These various parts may be affected singly, but more usually all are affected at the same time.

The susceptibility of the female genital mucous membrane changes in considerable degree according to the age. Thus in children the vulva and vagina are very easily infected. In adult girls the vagina is less susceptible, and in women who have had children a true gonorrhœal vaginitis is seldom seen.

According to Jadassohn, the vagina hardened by habitual sexual intercourse is only exceptionally infected.

Gassmann (1901) states that gonococcal infections of the uterine mucous membrane or of the tubes and ovaries are seldom observed in infancy, probably due to the fact that in infancy the cervix is still firmly sealed. In adult women, on the other hand, the mucous membrane of the cervix and the uterus is infected with great facility.

Bumm (1884-1897) pointed out that the vaginal mucous membrane, so susceptible to attack in infancy, became quite immune after puberty. Subsequently, however, Döderlein (1892), Welanders (1892), and Mandl (1897) proved that the gonococcus could settle down on the vaginal wall in the adult in isolated cases. This proof was obtained partly from sections. It is admitted by most observers, nevertheless, that gonorrhœal vaginitis is rare in adults.

According to the statistics of Baermann (1904) only 4.9 per cent out of 1214 gonorrhœal prostitutes had an infection in the vagina.

It is generally agreed that gonococci are most frequently found in adult gonorrhœal females in swabs taken from the urethra or the cervix, and that smears from the vagina are more frequently negative. Gurd (1908), on the other hand, frequently obtained cultures of the germs from vaginal swabs.

Glands of the Anterior Urethra.—Gonococcal infection of the mucous membrane of the urethra extends very readily into the various mucous diverticula, also into the ducts of the glands opening into the urethra, and into these glands themselves. By far the most common complication in this respect is an infection of the glands of Littre. Such an inflammation is called a *littritis* or *folliculitis*.

The pathology of this condition is well known. Suppuration follows the gonococcal infection, and in a short time the ducts become blocked and the pus is dammed up in the little glandular pouches. This retention causes enlargement and thickening of the walls of the Littre's follicles, so that they can even be palpated as small characteristic nodules.

According to Luys (1917) a *simple littritis* is the term applied where the inflammation does not extend beyond the gland walls. If, on the other hand, the inflammation spreads to the peri-glandular cellular tissue, the volume of the inflamed gland may reach the size of a cherry stone or a hazel nut, and the condition is then known as *folliculitis*. More correctly it should be called a peri-glandular cellulitis. This condition may develop into a peri-urethral cellulitis, and may end up in abscess formation (peri-urethral abscess). The pus may burst spontaneously outwards through the skin, producing a fistula from which the urine may escape on micturition. It is very desirable therefore to treat a *littritis* early, in order to prevent the spread of the infection into the peri-glandular tissues. This is accomplished by gradual dilatation of the urethra, accompanied by massage in order to express the infective contents of the glands. It may also be treated by slight dilatation combined with suction.

It is well known that the persistence of gonococci in the male urethra in spite of antiseptic irrigations is due to the fact that the germs get deep down into the glands and follicles, where the antiseptic is unable to reach them.

Keyes (1912) investigated 86 cases of clinically cured or nearly cured cases of urethral gonorrhœa. Twenty-seven cases were examined by smears and cultures, and the remaining 36 by the complement-fixation test. In 5 cases still believed to be infective clinically gonococci were found in smears. Twenty-six cases were considered to be suffering from a post-gonorrhœal catarrh, and in only 8 of these were gonococci detected. Out of 51 cases with only shreds or a slight haze in the urine, only 2 showed gonococci. Keyes estimated that the clinical error in judging apparent cure amounted to about 4 per cent. In 64 of his cases he found that the gonococci disappeared entirely in less than one year. In 7 cases they persisted for one to two years. In 9 cases which were supposed to have been cured from two to eighteen years previously, he was unable to detect gonococci, although misleading "degeneration" forms of staphylococci were found in one case. Only twice did he find gonococci in cases of urethritis of more than two years' duration.

Janet (1913) did not believe that the gonococci actually proliferated on the mucous membrane of the urethra itself, but that this occurred in foci in the interstices in the adjoining tissues. In the female, chronic gonorrhœa flourished indefinitely, because these extra-urethral foci were more numerous than in the case of men. Treatment which aimed at destroying the gonococci in the actual urethra always failed, because it did not reach the main focus, since the disease was not really a urethritis, but a constantly renewed infection of the urethra from these deep-seated foci. The germs were inhibited in their growth by a certain degree of local vaccination, also by phagocytosis, by the leucocytes, and by the columnar epithelial cells lining the urethra. The gonococci in the urethra were constantly being washed out, and their growth was inhibited by the growths of other germs.

Cowperitis. Luys (1917) states that although a gonococcal infection of Cowper's gland is rather rare, yet it should always be looked for, because in most cases it escapes observation. Moreover, when the germs are localised in these glands, the disease is apt

to last indefinitely, unless it is diagnosed and treated. The anatomy of Cowper's glands has been especially studied by Hogge (1903). The unusual length of the ducts explains the rarity of their infection, and moreover explains the impossibility of getting at the germs by means of antiseptics injected into the urethra.

Lebreton (1904) made a special study of Cowperitis, and found that it usually supervened during the third or fourth week of the attack of gonorrhœa, and that it was more often unilateral than bilateral. Two types of Cowperitis are encountered: (1) cases where the duct is not occluded, in which it is possible to massage the purulent contents of the gland into the urethra; (2) cases where the duct is blocked, and where in consequence massage fails to express the contents. The latter cases are obviously more difficult to treat. As in the case of the Littre's glands, the Cowper's glands may be infected with secondary organisms (staphylococci, pneumococci and diphtheroid bacilli, etc.), which accompany or follow in the train of the gonococcus. According to the researches of Couillard (1876), Tapret (1878), Englisch (1891 and 1894), and Hartmann and Lecène (1903), a tubercular infection of Cowper's gland may arise as a result of its invasion and devitalisation by the gonococcus. In such cases surgical extirpation of the gland is required.

Prostatitis.—This develops by direct invasion or emigration of the gonococcus into the prostatic ducts, when the disease has extended to the prostatic portion of the urethra. The gonococcal nature of prostatic inflammations in the course of an attack of gonorrhœa was definitely proved by the researches of Neisser (1885), and since confirmed by numerous other workers. The condition primarily consists of a catarrhal inflammation of the prostatic ducts and crypts; later it develops into a diffuse parenchymatous and interstitial inflammation of the whole organ. This may develop into further complications, such as sloughing of the peri-prostatic tissues, or formation of prostatic abscesses which may burst through into the surrounding parts. Thus according to the development of the infection we may subdivide gonococcal infections of this gland into—

(a) *Glandular or catarrhal prostatitis*, where only the ducts and crypts are affected. This condition is usually mild.

(b) *Parenchymatous prostatitis*, where the whole gland is inflamed, and where the ducts are often occluded. This more advanced condition is frequently accompanied by a marked inflammation of the peri-glandular tissues, and then we have what is known as an interstitial prostatitis.

(c) *Interstitial Prostatitis*.—When the infection has advanced to this extent it is common to get abscess formation.

(d) *Abscess Formation*.—The abscesses usually burst into the urethra, but may also open into the rectum or other neighbouring structures. Abscess formation is often accompanied by peri-prostatitis and cellulitis. Segond (1880) collected statistics of 140 cases of prostatic abscess. In 64 of these the abscesses burst into the urethra, and in 43 they broke into the rectum. Eight penetrated into the ischio-rectal fossa, 3 into the groin, 2 through the obturator foramen, and 1 through the great sacro-sciatic notch. One opened into the peritoneum, 1 into the cavity of Retzius, and finally 1 opened at the level of the false ribs.

According to Montagnin (1885) and Eraud (1886) 70 per cent of all cases of gonorrhœa suffer from prostatitis. Luys states that the chief cause of this complication is clumsy urethral injections, which are always harmful, also sexual excess, masturbation, fatigue, excessive exercise, and long journeys by carriage or by rail.

Luys (1917) further states that early glandular prostatitis produces no symptoms, hence it is important to examine the prostate in every case of gonorrhœa, and to massage it if necessary, thereby preventing the spread of the infection more deeply to the parenchyma and interstitial tissues. In phlegmonous, interstitial or parenchymatous prostatitis general symptoms occur, such as fever, tenesmus, dysuria, etc. Retention of urine due to inflammatory swelling of the prostate is not rare.

Prostatitis may further be divided into acute and chronic. Like all other inflam-

matory conditions, the chronic phase usually follows the acute. In certain cases, however, there is never any marked acute stage, but the onset of the chronic condition is gradual and insidious from the commencement.

Chronic gonorrhœal prostatitis is of extreme importance, as it is usually the cause of persistent gonorrhœa in the male. The gonococcus can exist in the depths of the prostate gland far away from the reach of any antiseptic urethro-vesical irrigation, and in spite of such treatment, a more or less constant exudate of pus comes down the prostatic ducts into the urethra, causing a persistent though small gleet. This discharge, containing a few gonococci, may give rise to repeated reinfections of the urethra itself. In such cases it is obvious that the only rational treatment is massage of the prostate to express the septic matter, combined with general measures such as vaccines, in order to raise the immunity of the patient.

According to the researches of Notthaft (1904) gonococci cannot exist in the prostate for a longer period than three years. Other workers, however, entirely disagree with his observations. Layne (1903), for example, found gonococci in the prostatic secretion of a series of chronic cases as long as seven to eight years after the original infection, and in one patient after a period of eighteen years.

Zigler (1916) reported on a case of persistent gonococcus infection of eleven years' duration.

In chronic latent cases of gonorrhœal prostatitis it is often difficult to detect gonococci in the expressed secretion after massage. Evidently the germs often exist in small numbers.

Wolbarst (1909) made 240 microscopic examinations of the prostatic secretion after massage in 35 cases. He concluded from his observations that a man might be apparently cured of gonorrhœa and have no symptoms, yet the prostatic secretion might still yield gonococci. He was even able to find the germs in clear urine without shreds. He believed that the gonococcus could persist in the prostate for many years without necessarily producing any symptoms. The only way of ascertaining whether or not a given prostate was free from the disease was to make a large number of examinations of the secretions obtained after massage, and after stimulation and irritation by silver nitrate, etc.

Saxe (1909) found that in 150 cases of chronic gonorrhœa of six months to eighteen years' duration 6 per cent showed prostatitis. The older the infection the more frequent was the prostatitis. Out of 108 cases of chronic prostatitis, 31 or 28·7 per cent showed gonococci in the expressed secretion. The older the infection the more difficult it was to find gonococci in the prostate. After three years, gonococci were rarely found even after the most persistent efforts to detect them, but many thorough examinations were required before one was justified in pronouncing that the germ was absent.

Mixed infections occurred in 86 per cent of the cases which he studied. The gonococcus alone occurred in only 5 cases out of 108, and all of these 5 cases were of less than one year's duration. The older the case the more prevalent was the mixed infection. Staphylococci occurred in 74 per cent, bacilli in 28 per cent, Gram-positive diplococci in 10 per cent, and streptococci in 7·6 per cent of cases with mixed infection. The absolute need of microscopic examination of the prostatic secretion was shown by the fact that palpatory signs were absent in 38 cases (35 per cent), while 13 cases (12 per cent) showed absolutely clear urine, although the smears showed a prostatic infection.

Rathbun and Dexter (1909) claimed after a series of clinical and bacteriological investigations—

(1) That there are numerous cases of uncured gonorrhœa which have no subjective symptoms or apparent objective symptoms other than those which can be determined by cultures made from the secretions obtained from the genito-urinary tract.

(2) That freedom from pus cells in the smear from an expressed prostatic secretion is by no means an evidence of cure of chronic prostatitis, nor is the presence of pus cells in such a smear an indication of gonorrhœal infection of that gland; nor is the presence

of a Gram-negative diplococcus in the smear of this secretion a positive indication of the existence of gonorrhœa of the prostate. The nature of these isolated Gram-negative diplococci could only be definitely ascertained by cultural methods. Finally they concluded that the number of cases of uncured and incurable gonorrhœal prostatitis was far in excess of what most clinicians were ready to believe.

Stein (1910) pointed out the fact that apparently cured cases of gonorrhœa were sometimes encountered in which microscopic examination showed that gonococci still persisted.

Faxton Gardner (1910) contributed a paper on the pathological anatomy and treatment of suppuration in the prostate due to the gonococcus.

Asch (1911) reported on the occurrence of acute and chronic healthy gonococcus carriers.

The writer is more or less entirely in agreement with the above observations of Wolbarst, Saxe, Rathbun and Dexter. The truth may be summed up more or less accurately as follows :—

(a) Gonorrhœal infection of the prostate is very common.

(b) It is very difficult to eradicate, and if not treated energetically it may exist for years in a more or less chronic or latent condition, the only symptoms being an occasional recurrent gleet.

(c) In a very large percentage of cases, secondary organisms (chiefly staphylococci and diphtheroid bacilli) exist in the prostate along with the gonococcus.

(d) In some cases the gonococci gradually die out, but the secondary organisms remain, causing a low form of chronic catarrh.

(e) Gonococci can only be detected in the prostatic secretion by frequent and careful microscopic or cultural examination of the expressed secretion after massage.

(f) In smears carefully stained by Jensen's method, Gram-negative diplococci are practically certain to be gonococci. Pneumococci are easily decolorised by Gram's method and may be mistaken for gonococci in carelessly stained smears.

(g) The most delicate method of detecting the existence of latent gonorrhœa is by the complement-fixation test.

(h) The only rational method of treating gonococcal prostatitis is by massage and gonococcal vaccine, since no irrigation can reach this deep-seated infection. Where secondary organisms are present, mixed vaccines of the latter must be administered.

(i) One cannot expect to eradicate an old chronic gonorrhœal prostatitis by massage and vaccines under a period of two to three months, but with perseverance the most refractory cases may eventually be cured.

(j) When no gonococci or other organisms can be detected in smears, and when the complement-fixation test is negative, the patient may be pronounced fit to marry. Where secondary organisms alone exist vaccines of these organisms may be given alone. It is advisable, however, always to include gonococcal vaccine in the mixed vaccine.

Ballenger (1910) reported on cases of chronic non-gonorrhœal infections of the prostate.

The writer has seen at least two such cases where the prostate was severely infected with staphylococci following injections of lysol solution. In both cases the solution was injected into the urethra from a syringe by the patients themselves as a prophylactic against gonorrhœa after connection. In these patients the urine was cloudy and contained large shreds. Microscopic examination of the deposit showed pus cells and enormous masses of staphylococci, both extra- and intracellular.

In many patients chronic gonorrhœal prostatic infections lead to a condition of so-called sexual neurasthenia, which may further exert a strong prejudicial influence on the patient's health.

Gonorrhœal Vesiculitis (Spermato-cystitis).—Quite a common complication of gonorrhœa is a purulent inflammation of the seminal vesicles. In these cases the pus some-

times breaks through this organ into the neighbouring peritoneum. Further, on account of the very vascular nature of the walls of the vesicles, the gonococci are very liable to get into the blood stream and thereby cause a general metastatic infection. Amongst others, Wynn (1905) and Prochaska (1905) described a gonorrhœal general infection accompanying a purulent inflammation of the seminal vesicles. In one of Prochaska's cases there developed a purulent gonorrhœal meningitis as a sequela of a vesicular infection, and he succeeded in cultivating the gonococcus from the tenacious meningeal pus, as well as from the purulent matter in the vesicles themselves.

Many authors (see Chapter XXIII., on Metastatic Infections) have drawn attention to the fact that metastatic gonococcal infections have their origin in a vesicular focus.

Colemore (1912) contributed a paper on "Chronic Gonorrhœal Semino-vesiculitis," but the author has been unable to obtain access to his work.

According to Luys (1917) spermato-cystitis is a common complication of gonorrhœa. It may be unilateral or bilateral, and is always a tedious and serious complaint to treat. He believes that intercourse during an attack of gonorrhœa is the chief cause of infection of the vesicles.

Very often a vesiculitis causes little discharge, beyond a little moisture about the meatus or a drop in the morning. There may be some vague pains in the perineum or in the lower abdomen, or in the loins. They are usually more marked during defæcation, and radiate along the urethra, the glans, the testicles, and sometimes the kidneys. They may assume the character of "colic" (vesicular colic), and be mistaken for an attack of appendicitis or of renal or ureteric colic. Reliquet (1880) described this condition, and stated that the pain was often like cramp, and radiated along the urethra to the glans as well as backwards to the anus. This vesicular colic he considered to be due to a mechanical obstruction in one or both ejaculatory ducts, and to be absolutely comparable with renal colic.

The changes in the generative functions are of great importance. "Painful erections and painful pollutions are sometimes complained of, or the ejaculation is premature." The diseased seminal vesicle expels the semen in the same way as an inflamed bladder gets rid of its urine (Guiard). Some cases become impotent. The pathological changes in the seminal vesicles and in their excretory ducts may bring about sterility. Occasionally the semen is blood-stained. This condition, which is called "hæmospermia," is only characteristic of a lesion of the seminal vesicles if the semen and blood are intimately mixed. This condition must not be confounded with a little bleeding from a urethral ulcer occurring during a seminal discharge. When the blood comes from the seminal vesicle (hæmospermia) the semen is usually yellowish and rusty. When the blood is very abundant and has lain in the vesicles for some time the colour is darker, and may even be as black as ink.

Examination of the urine, which should always be passed into four glasses, often enables one to make a provisional diagnosis of vesiculitis. If the urethral discharge ceases after a series of irrigations into the bladder, and if after this the urine continues to be uniformly turbid in all four glasses, a vesiculitis is probable, and a local examination is indicated. Frequency of micturition is not uncommon with vesiculitis, and there may be pain when the bladder is full, or during the act of micturition.

Phosphaturia is generally present. These phosphates apparently ooze from the seminal vesicles themselves, and do not come from the kidney.

After massage of the prostate and vesicles, if gonococcal vesiculitis is present one usually finds by microscopic examination of the expressed secretion red blood cells, pus cells, and spermatozoa; gonococci are sometimes seen, and quite frequently staphylococci and diphtheroid bacilli.

Acute gonorrhœal vesiculitis is often accompanied by marked general symptoms, with a considerable amount of fever. There is often general malaise, pallor, fatigue, and loss of appetite. Palpation per rectum is very painful, and may even cause the

patient to faint. It is necessary to palpate very gently, otherwise a violent attack of fever may follow after the digital examination. The prognosis in spermato-cystitis should be guarded. Many cases get well without much trouble. An abscess may form in some cases and burst into the peritoneal cavity, causing a fatal peritonitis. Kocher (1887) and Wildbolz (1903) published accounts of cases of this nature. Vадja reported a case where the vesicular abscess burst into the rectum, but this is more rare. As a rule they open into the urethra or the bladder.

The relative thinness of the walls of the seminal vesicles and the richness of their vascular supply explain readily why a spermato-cystitis is so dangerous. Luys believes that a gonococcal inflammation of the vesicles is the starting-point of a general systemic infection such as rheumatism, myelitis, etc., in practically every case.

Amongst the other complications observed in the course of a protracted gonorrhœal vesiculitis, Luys mentions the occurrence of attacks of pain along the ureters. Picker (1908) was one of the first to point out this symptom. They are often very severe, and simulate renal colic, so much so that a wrong diagnosis is apt to be made, unless one is acquainted with the history of the case. The origin of these pains is to be found in a compression of a portion of the ureter, either directly through the inflamed vesicle, or more usually through the peri-vesiculitis which is commonly present in this condition. The lumen of the ureter may become partly obliterated, and the resulting obstruction to the flow of urine may give rise to the pain of renal tension which is observed in renal colic. Spermato-cystitis is very generally accompanied by an inflammation of the vas deferens, and this often leads to an irritation of the peritoneum. The upper part of the seminal vesicles is in contact with the peritoneum, and the vas deferens is also covered by it for a considerable part of its course. When the peritoneum becomes inflamed, pain occurs in the lower part of the abdomen and may finally become generalised all over the peritoneal cavity. Further signs of peritonitis are retching, nausea, vomiting, rapid pulse, and rapid breathing. The condition is often mistaken for appendicitis, as pointed out by Le Für (1911). On examination the vas deferens is found to be enlarged; it often resembles a thick, hard cylinder which projects through the superficial inguinal ring.

Lastly, vesiculitis and epididymitis frequently go together, and it is well to inform patients who are suffering from an inflammation of their vesicles of this fact.

Luys further states that in all cases the course of a spermato-cystitis is a protracted one. Its minimum duration is two months, and it often lasts longer. The treatment naturally varies according as the inflammation is acute or chronic.

In acute gonorrhœal spermato-cystitis local intervention should be avoided. Not only is it certain to give rise to severe pain, but it is also apt to bring about a systemic infection. Massage of acutely inflamed vesicles is to be condemned. The best treatment appears to be rest in bed, the intake of large quantities of fluid, urethro-vesical irrigations with weak permanganate, and hot rectal irrigations, which are especially valuable.

The chronic cases are treated by means of massage of the seminal vesicles. This is carried out after the bladder has been filled with fluid from an irrigator. If done efficiently, it frees the affected organ from the purulent débris, which is subsequently washed away when the bladder is emptied. In certain instances the vesicles are situated at a very high level, and are beyond the reach of the finger. Electric massage, carried out with Feleki's instrument or a similar apparatus, can then be resorted to with advantage. This massage treatment should be continued until the urine has become clear. When this has been achieved dilatation should be resorted to, using Frank's irrigating dilator towards the finish of the treatment. Lastly, urethroscopic examinations should be made in order to verify the condition of the verumontanum and of the ejaculatory ducts.

Finally, Luys states that a vesiculitis can only be considered as cured when all pain in the region of the vesicles has disappeared and when no longer any purulent débris comes away on massage.

Belfield (1920) states that in the majority of cases of gonorrhœa the vesicles become infected within the first month, and he points out that the ordinary irrigations used in treatment never get at this infection in the vas and vesicles. In his paper he gives sketches and skiagrams, and strongly recommends the importance of irrigating the vas and vesicles with a 5 per cent solution of collargol.

Keyes (1920) found that the operations of vesiculotomy and vesiculectomy were most discouraging, and only gave good results occasionally.

Epididymitis.—This is a very common complication in gonorrhœa. According to Luys it is met with in about 25 per cent of all cases. This condition is directly due to the gonococcus. Baermann (1903) demonstrated the presence of the germ by culture methods in a large number of acute cases.

Routier, Grosz (1897), Collan (1897), Colombini (1898), Hartung (1898), and Witte (1899) all failed to cultivate gonococci from the pus obtained from purulent cases.

Scholtz (1903) states that the germ can more often be cultivated from very early cases, but as a rule at this stage there is little or no pus to be obtained by puncture.

The writer has frequently cultivated the gonococcus from purulent cases of epididymitis, by smearing the pus on human-plasma-glucose agar. Very often, however, the cultures were apparently sterile until the fifth, and in some cases even the tenth day of incubation, when one or two small colonies of gonococci appeared. It is a mistake, therefore, to discard the culture as negative until it has been incubated for at least ten days. In several cases no gonococci developed, but minute colonies of a clubbing diphtheroid bacillus were grown from 2 cases (see Pl. VII., No. 4).

According to Luys, epididymitis usually occurs during the third, fourth or fifth week of the gonorrhœal attack. It is generally supposed that the gonococcus penetrates from the urethra to the epididymis by way of the vas deferens. From clinical observations, as well as experiments on animals, Nobl (1901) believed that the mucous channel of the vas deferens was the only route by which the gonococcus could spread from the posterior urethra to the epididymis. Ullmann (1901), however, maintained that the germs could penetrate to the testicle by way of the lymphatics, and Rosenthal considered that the epididymis was infected in this manner.

Whatever be the chief route of infection, there can be no doubt that the epididymitis is a true gonococcal inflammation, and that it is not caused by the circulating toxins of the germs. Further, it would appear that secondary organisms (mixed infection) do not play much part in the disease, since, as a rule, the cultures obtained are purely gonococcal. Occasionally, however, as the writer has already mentioned, diphtheroid bacilli appear to be present.

Bonner (1913) described an acute epididymo-orchitis due to *Bacillus coli*. One must always be prepared also to exclude a tubercular infection. Tubercle bacilli are apt to settle down on an epididymis which has been devitalised by a previous gonorrhœal attack.

According to Luys (1917), the first symptom of epididymitis is usually a heavy feeling about the scrotum, and on palpation the tail of the epididymis is found to be somewhat enlarged. The pain which comes on subsequently is often so acute as to make the patient moan and shriek. As a rule it lasts three to five days. It then diminishes in intensity and disappears fairly rapidly. The testicle is always swollen; the skin over it is red, hot and tense. Behind the testicle, which has retained its peculiar sensation, a hard mass is to be felt which is very tender on pressure. A certain degree of hydrocele is very commonly present. The general health is always affected, and there is fever, rising to 100° to 102° F., which lasts four or five days, and then gradually disappears. The duration of the illness is from two to three weeks on the average. As a rule the inflammation subsides without leaving any trace; occasionally, however, a nodule remains in the tail of the epididymis, and very often the spermatic cord remains thickened for a considerable time. Occasionally the other testicle may become infected, and it is not a rare occurrence to get a double epididymitis at one and the same time. The prognosis is good, and a cure is usually

observed after two to three weeks. The danger is the functional damage which may result, since in cases of bilateral epididymitis the spermatozoa may disappear completely, and thus render the patient unfit to beget children.

Medical Treatment of Gonorrhœal Epididymitis.—Various treatments have been advocated by different authors; all are agreed, however, that complete rest in bed is essential during the acute or fever stage. The patient should be put on light diet, and the bowels should be well opened. It is also good to raise the scrotum to the level of the abdomen by means of a suspensory bandage. Soothing local applications are of value, such as hot fomentations, or an ice bag, or the alternate use of both. The local applications soothe the pain, but do not shorten the duration of the disease.

Du Castel (1898) sprayed the inflamed epididymis daily with methyl chloride, or else applied it on cotton-wool.

Luys states that ethyl chloride may be used instead to relieve the pain.

Bettmann (1899) advocated the use of cotton wool compresses soaked in a mixture of one part of methyl salicylate and two parts of olive oil.

Picot (1899) recommended sodium salicylate internally in gramme doses four times daily. He found that this drug relieved the pain. It should be continued for eight to ten days.

Galatz (1902) recommended the use of the following ointments :—

	Vaseline	30 grammes
	Ichthyol	4 „
	Guaiacol	2 „
or							
	Lead iodide	2 grammes
	Cold cream	30 „

Bruck (1910) advocated that in every case the scrotum should be sterilised with iodine and then incised. This procedure evacuates any fluid, relieves the tension and pain, and also reduces the fever. After the fever subsides he gave gonococcal vaccine with satisfactory results.

Saynisch (1913) reported good results in the treatment of epididymitis with gonococcal vaccine (arthigon) in combination with ichthyol dressings.

Very excellent results have been obtained in epididymitis cases with gonococcal vaccines (see chapter on vaccine therapy). Some authors also claim good results with gonococcal anti-serum; *vide* chapter on Serum Therapy.

Gonorrhœal Cystitis.—Gonorrhœa can spread backwards from the original urethral infection to the mucous membrane of the bladder in both sexes. Previously it was usually considered that infection of the bladder was due to secondary organisms, such as *Bacillus coli*, etc., but most observers now agree that the gonococcus is also capable of producing a cystitis by itself. Wertheim (1895) described a case of pure gonococcal cystitis in a woman.

Finger, Ghon and Schlagenhauser (1894), and also Wossidlo (1903), were able to demonstrate the presence of gonococci in the urine obtained direct from the bladder, and also in the bladder mucous membrane.

Further cases of pure gonorrhœal cystitis have been described by Barlow (1893), Audry (1894), Krogus (1893), Rovsing (1897), Bierhoff, Heller (1901), and Jadassohn (1906).

Histological researches by Finger (1905) on gonococcal cystitis have shown that the vesical epithelium undergoes desquamation, and that it is replaced by proliferation of the sub-epithelial tissues. The vessels of the latter are congested and filled with leucocytes, most of which are laden with gonococci.

According to Luys, cystoscopic examination in gonorrhœal cystitis shows that the

mucous membrane is in a state of generalised diffuse inflammation, which is sometimes accompanied by a more or less marked oedema. In places raised follicles, represented by acuminated dark red spots, are visible on the mucosa. The lesions are usually most pronounced near the internal sphincter at the level of the trigone. This author further states that the condition usually supervenes upon an inflammation of the posterior urethra. It comes on most frequently about the third or fourth week of the infection, and is nearly always the result of direct contamination by means of forcible injections or instrumental interference. In a few cases violent exercise, sexual excess, riding on horseback or in a carriage, whilst the gonorrhoea is still in the acute stage, may lead to implication of the bladder.

Symptoms of Cystitis.—These are the same as in any other form of infective cystitis, viz. frequency of micturition, with vesical tenesmus. In severe cases the patient may wish to micturate even every five minutes. This condition is aggravated by walking or standing, and is considerably relieved when lying down. Micturition is painful, the pain being most marked at the end of the act when the last drops are being expelled.

The urine, as a rule, is cloudy and purulent. When passed into four glasses, the last sample is always the most turbid. The last few drops of urine passed frequently contain blood.

Prognosis.—The acute cases usually last about eight to ten days. Sometimes, however, they fail to clear up and pass into a more or less chronic state. Relapses are very common. A tubercular infection is sometimes liable to follow upon a chronic gonorrhoeal cystitis, in which case it is rather difficult to distinguish between the two infections. If there is any doubt on this matter, the urine should be centrifugalised. Part of the deposit obtained should be injected into a guinea-pig, and the remainder stained by the Ziehl-Neelsen method and examined microscopically. The guinea-pig should be examined some two to three weeks later to see if any tubercular nodules have developed near the site of injection.

Treatment.—Rest in bed, with a fluid diet. Hot fomentations over the bladder help to relieve the pain.

Weinbrenner (1915) maintained that it was important to render the tissues and the urine as acid as possible. Thus he advocates that all alkaline waters should be avoided, and he also forbids vegetables and fruits because of their alkaline salts. He recommends that animal food should be given. Alcohol is prohibited.

Whatever may be the practical results of this treatment the writer is inclined to believe that it is wrong from the theoretical point of view. It has already been pointed out that weak acids preserve the gonococcus, whereas weak alkali is very destructive to the germs because of its power of dissolving them. Theoretically, therefore, one would recommend that the urine should be made as alkaline as possible.

Luys (1917) recommends that the patient should drink *infusum uvae ursi foliorum*, which is prepared in the same way as tea, and sweetened by means of the following syrup :

Syrup of tolu	300 grammes
Benzoate of sodium	15 "

One teaspoonful per cup of infusion.

He also believes that good results are obtained with sandal-wood oil and the various balsam preparations ; also urotropine or helmitol in doses of 1.5 to 2 grammes per day. If the cystitis is accompanied by phosphaturia, he recommends acidifying the urine to dissolve the phosphates. In such cases he prefers uraseptine to urotropine, because the former acidifies the urine.

Local treatment should be deferred until all acute inflammatory phenomena have subsided. Later, weak irrigations of potassium permanganate may be given. When all urethral discharge has subsided, good results are obtained by instillations into the bladder of 1 or 2 per cent silver nitrate every other day. If the nitrate is not well borne, and

causes excessive pain, it can be replaced with advantage by an organic silver salt, such as protargol or argyrol.

Gonococcal Pyelitis and Pyelo-nephritis.—In conjunction with gonorrhœal cystitis, a further extension of the infection may pass to the ureters, to the pelves of the kidneys, and even to the kidneys themselves. Although in many cases where this spread of the disease has occurred, secondary pyogenic organisms such as staphylococci and *B. coli* may be found, yet there is no doubt that a pyelitis and a pyelo-nephritis can be caused by the gonococcus alone. Pure gonococcal cases have been described by Bockhardt (1886), also by Mendelssohn, Ashara (1898).

v. Zeissl (1903) and Wossidlo (1903) succeeded in demonstrating the gonococci in the pus from the pelvis of the kidneys, or in the kidney abscesses, not only microscopically, but also by cultural proof. Further cases of this kind were described by König (1900).

Brandsford Lewis (1900) reported on this extension of gonorrhœa, and later 5 cases were observed by Sellei and Unterberg (1907) in which *B. coli* was found in conjunction with the gonococcal infection. They maintained that gonococcal pyelitis was an ascending process, and that the infection did not occur through the blood stream. A cystitis was always present first, and although the gonococcus alone could cause a pyelitis, in the majority of cases the infection was a mixed one.

Hagner (1910) reported 27 cases which came under his own personal observation. Sixteen of these showed a mixed infection, whilst 9 were purely gonococcal.

Lehr (1912) reported on a case of gonorrhœal pyelitis. He states that he was only able to find in the literature an account of about 20 cases. In 5 of these the gonococci were only obtained from the urine. In 2 the condition was due to a mixed infection, and in 4 others no cultures were made. In 1 case a nephrectomy was done, and a definite diagnosis made from the pus in the pelvis. In 4 further cases the nature of the disease was only recognised at the autopsy. Finally, in only 4 of the reported cases were cultures of the gonococcus obtained during the course of the disease.

In spite of the scarcity of cases reported in the literature Lehr believes that this complication is more common than one would suppose.

The case which he himself described occurred in a man aged 27. He complained of a urethral discharge and painful micturition. He gave a history of two gonorrhœal attacks eight and six years previously from which he recovered completely without complications. He had never had typhoid fever or Bright's disease, etc. The urethral discharge was scanty; urine showed pus cells and numerous gonococci in all three glasses. There were no casts, but there was marked terminal hæmaturia at the end of micturition. The prostate and seminal vesicles seemed normal, since there was no apparent enlargement and no tenderness. The temperature reached 100° F., with a pulse rate of 84 per minute. The patient indulged in alcohol, and had an acute exacerbation of the trouble, with hæmaturia and great frequency of micturition.

Cystoscopic examination showed that the mucous membrane of the bladder was inflamed over its entire surface. It had a yellowish-red colour. There was no inflammation around the ureteral orifices, but from the left orifice pus and urine were seen to escape. From the right orifice normal urine exuded. The left ureter was catheterised, and cultures made from the purulent urine on ascitic agar gave pure growths of gonococci.

Gonococcal vaccine was then given in doses of 50 to 100 millions, and 20 c.c. of 30 per cent argyrol was injected into the ureter. No improvement occurred. Later 20 c.c. of 1 in 3000 silver nitrate was injected per the left ureter with slight improvement. Still later the pelvis of the kidney was washed out with 1 in 5000 silver nitrate, and this was repeated on two occasions at three-day intervals. A complete and rapid recovery resulted. The kidney itself was not involved.

Lehr points out that in this case the onset was insidious. There was little evidence of toxæmia, and the fever was only slight.

Harpster (1913) communicated two papers on renal gonorrhœa. According to Luys

(1917), the gonococcus may reach the kidneys through the ureters, through the blood stream, or through the lymphatics.

(1) *Through the Ureter*.—This route is perhaps the most common one. Murchison has described cases in which a gonorrhœal cystitis was followed by an inflammation of the whole ureter. In most cases the ascending infection supervenes upon retention, whether the latter is caused by a stricture of the urethra or by an inflammation of the prostate. The ureteric orifices are enlarged and gape in these cases. The urine thus flows backwards from the infected bladder, and the gonococci are able to find their way to the kidney.

(2) *Through the Blood Stream*.—This route is the only feasible one when there is no concomitant gonorrhœal cystitis.

(3) *Through the Lymphatics*.—The gonococci set free from a prostatic abscess can travel along the ureter into the peri-renal tissue, and can subsequently invade the kidney itself.

Predisposing Causes.—Luys maintains that the abuse of balsam preparations irritates the renal epithelium and renders it more susceptible to attack by the gonococcus.

Signs and Symptoms.—Gonorrhœal pyelo-nephritis usually begins with shivering and fever amounting to 39° to 40° C., but the onset may be insidious, as shown in Lehr's case. If pus is present, and if the lumen of the ureter is sufficiently obliterated to bring about the retention of the pus in the renal pelvis, very high fever is common. When such retention occurs, the kidney involved becomes painful. This pain may radiate along the ureter to the bladder and even to the penis, or it may be referred to the loins. The condition may be unilateral or bilateral. Further retention of the pus may lead to gastric disturbances and violent headaches, as well as diarrhœa alternating with constipation, loss of appetite, and a coated tongue.

Palpation of the kidneys does not give much information as a rule, but it may show that the pain is limited to one kidney.

Diagnosis.—This is chiefly settled by microscopic examination of the urine deposit, which consists of pus cells, red cells, casts, renal cells, gonococci and perhaps other organisms. Albumin is usually present. Final evidence is obtained by cystoscopy and catheterisation of the ureters.

Treatment.—Consists of rest in bed on a low diet, such as only milk or even water. The patient should be purged, and urotropine 1·5 grammes daily is indicated. Alcohol should be avoided.

Kelly and Casper (1898) recommended irrigation of the renal pelvis with boric lotion, or with a 0·1 per cent solution of silver nitrate through a ureteric catheter. More serious cases require a nephrotomy or even a nephrectomy.

Finally, certain authors have obtained good results with vaccine or serum therapy; *vide* Chapters XXXII. and XXXIII.

Ano-rectal Gonorrhœa (Gonorrhœal Proctitis).—The gonococcus is capable of infecting the rectum, and according to various published statistics this mucous membrane is rather susceptible to attack.

Bumm (1884) was the first to demonstrate the presence of the germ in a purulent discharge from the rectum.

Horand (1888) reported 8 cases in which the disease had been caused by direct spread from the genitals.

Frisch (1891) made post-mortems on individuals who had been suffering from rectal gonorrhœa for six months and found gonococci not only in the pus, but also in sections of the rectum.

Tuttle (1892) published 3 cases in which microscopic examination of the rectal mucopus showed gonococci.

Hartmann (1895) quoted a case of gonorrhœal ulceration of the anus, in which the gonococcus was present.

Mermet (1896) wrote a paper on the literature of this complication.

Griffon (1897) reported a case in a young man of nineteen.

Baer (1896) found that the rectal mucous membrane was infected in 31.5 per cent of all cases of gonorrhœa in women, whilst Huber (1897) placed the figure at 24.5 per cent. The rectum alone was infected in 10.4 per cent of Baer's cases, and in 17.9 per cent of all those examined by Huber.

Eichhorn (1909) ascertained that the rectum was involved in 30.6 per cent of the gonorrhœal women who attended his clinic.

Flügel (1905) in a series of 56 cases of vulvo-vaginitis in little girls found that the rectum was infected in 20 per cent.

Jullien (1905) maintained that ano-rectal gonorrhœa occurred in 5 per cent of all cases, and that it was much more common in women than in men.

Brunswick-le-Bihan (1907) stated that three complications, which were by no means rare, might occur in gonorrhœal infections of the rectum. These were, acute peri-rectitis, chronic peri-rectitis, and finally rectal stricture analogous to syphilitic stricture in this situation.

Stümpke (1914) wrote a paper on gonorrhœal granulations around the anus and perineum. He states that Klingmüller (1910) had described 6 cases in which there was a proliferation of tissue in the perineum or anus in women suffering from a gonococcal infection of the urethra, cervix, or rectum. In one case there were also condylomata. The excrescences were somewhat like a cock's comb. Some were painful, but none of them were susceptible to bleeding. In most cases they had to be excised.

All are agreed that the incidence of gonococcal infection of the rectal mucous membrane is much higher in women than in men, and this is no doubt due to the fact that in the female the rectum, vagina, and urethra are in close anatomical relationship. Thus the rectum is very easily infected by the downward flow of the purulent discharge from the urethra, vagina, and vulva. In the male the chance of such a local spread is much more remote. Direct infection of the rectum from perverted sexual intercourse is rather rare in women, but occurs more frequently in men.

Verchère (1894), however, maintained that this direct infection was by no means rare, as he ascertained that few prostitutes, if any, resisted such perverted sexual intercourse, and he declared that the habit was quite common.

According to Luys (1917), women have been known to infect themselves by taking an enema through a cannula which had been used previously for a vaginal douche by some other woman who was suffering from gonorrhœa; and he quotes Rollet's case in which a man who acquired gonorrhœa inoculated his rectum with his finger. This man, who suffered from chronic constipation, had been in the habit of introducing his forefinger into his rectum in order to induce defæcation. There are still other routes by which the rectum may be infected: Picker (1905) drew attention to cases which supervened upon abscesses of Cowper's glands, of the prostate, and of the seminal vesicles. In such cases the gonococcus may spread to the rectum or peri-rectal tissues directly through the lymphatics, or by the actual bursting of the abscess into the anal canal.

Signs and Symptoms.—In most cases these are mild and cause little inconvenience; in fact, there may be no symptoms at all. On this account the condition is very frequently overlooked unless a very careful examination is made.

Luys (1917) says that it is a great mistake to expect the anal and peri-anal tissues to be bathed in pus, or to be violently inflamed and excoriated. The discharge, which is scanty, is brownish, and the gonococcus is difficult to find amongst the huge number of other micro-organisms present.

Jullien gives the three important signs of ano-rectal gonorrhœa as follows:—

(1) *The drop.*—This may be obtained in women by introducing the finger into the vagina and pressing from above downwards on the recto-vaginal septum. A drop of pus may be expressed in this way in which gonococci may be found.

(2) *The fissure*.—This is usually found at the posterior end of the anus. It is narrow and superficial, and usually hidden in a fold of the mucous membrane. It seldom gives rise to bleeding, and takes a slow and indefinite course.

(3) *The condyloma* is the most characteristic sign of ano-rectal gonorrhœa. It is single, prominent, elongated, thin, shiny, soft, and almost painless.

The complications described by Brunswick-le-Bihan have already been mentioned, viz.: (a) *Acute peri-rectitis*, which is really an ischio-rectal abscess.

(b) *Chronic peri-rectitis*, which is characterised by the formation of a firm, hard sheath of induration around the rectal walls. This gives rise to troubles in defæcation, tenesmus, difficulty and pain in emptying the rectum. It is often very persistent and difficult to treat.

(c) *Rectal stricture*.—This condition, according to le-Bihan, is more common than is generally imagined, and occurs more often after gonorrhœa than after syphilis.

Luys states that the course of ano-rectal gonorrhœa is very similar to that of a gonorrhœal urethritis. The inflammation first causes a thickening of the coats of the rectum, and when this begins to shrink and contract a cylindrical obstruction results. The prognosis in rectal stricture should be guarded. The condition is very difficult to treat, and the patient eventually suffers from persistent diarrhœa, which weakens and exhausts him.

Luys (1910) describes a condition of *proliferative gonococcal rectitis* which is characterised by the formation of papillomatous growths, which may either be sessile, pedunculated, or condylomatous in type.

Treatment.—This should be commenced as early as possible. Irrigate with weak potassium permanganate.

Fischl recommends daily injections of an iodipin mixture, which consists of 100 grammes of the original 20 per cent iodipin solution and 200 grammes of sterile olive oil. He injects 10 c.c. by means of a syringe fitted with a curved soft indiarubber nozzle. He claims for this treatment that it leads to softening and resorption of the indurations and infiltrations, both in acute and in chronic cases. Luys states that if the anal sphincter is implicated, gauze ribbon, medicated with borax or iodoform, should be introduced into the anus. When the rectum is seriously involved the best treatment is local therapy carried out under the control of Luys' rectoscope.

Klingmüller (1910) describes 8 cases of condylomatous proliferation around the anus or on the perineum of women with a gonorrhœal infection in the rectum. He also describes a case of a granulomatous growth on the prepuce of the male. He ascribes these proliferations to the gonococcus.

Boas (1919) found the rectum involved in 14 out of 88 women with gonorrhœa. It did not cause any special subjective or objective disturbance, and it proved amenable to treatment in most cases. Irrigations with hot potassium permanganate retained in the rectum were very useful. He urges the necessity for examining for involvement of the rectum in every case.

Gonorrhœa buccalis.—Gonococcal affections of the oral and nasal mucous membrane are very uncommon, and may be regarded to a certain extent as rare curiosities. Nevertheless, it has been proved that such infections can undoubtedly occur.

Horand (1885) related the case of a medical student who had a coitus buccalis with a prostitute, with the result that he received an oral infection of gonorrhœa which lasted two weeks.

Cuttler (1889) published the case of a woman who developed a pseudo-membranous stomatitis after similar unnatural coitus with a gonorrhœal subject. The false membrane contained gonococci.

Petit (1889) and Honnora (1889) described cases of gonorrhœal stomatitis which were characterised by a swelling of the tongue, by greyish, rounded spots on the buccal mucous membrane, and by a fœtid breath.

Rosinski (1891) succeeded in cultivating the gonococcus from a few cases of stomatitis in newly-born infants, and thereby was really the first to establish definitely the occurrence of a gonococcal infection of the oral mucous membrane.

Kast (1894), Jesionek (1898), Colombini (1901), Vines (1903), and Jürgens (1904) each described cases of gonorrhœal stomatitis in adults in whom typical gonococci were demonstrated in the oral secretion by microscopic examination. In Jürgens' case the lesions were most marked at the free border of the gums, which were covered with a greenish-grey and very fœtid deposit of pus. The buccal mucous membrane was, moreover, swollen, inflamed, and painful, so that the patient had difficulty in opening and closing his mouth. Salivation was so free that the pillow was saturated overnight. The condition improved under local applications of 0.15 per thousand corrosive sublimate solution. The gonococcus in this case was found in film preparations, and the findings confirmed by culture on Wertheim's medium.

Kimball of New York (1903) described a case of gonococcal pyæmia which had its starting-point in the mouth.

Malherbe (1911) reported on a case of oral gonorrhœa in which an intense stomatitis developed, and which was accompanied by violent pain and inability to swallow. The pus contained gonococci, and the buccal mucous membrane was smooth as if varnished. The lips were covered with a large number of small, irregular, superficial ulcerations, and the gums were œdematous and loose around the margins of the teeth, where there was a considerable amount of pus. The hard and soft palates were red but not inflamed. Buccal irrigations with 1 in 4000 solution of potassium permanganate, and painting the ulcerations with a 2 per cent solution of chromic acid in water, gave great relief, and effected a cure in five days.

Stein (1913) and Farbach (1914) contributed further papers on gonorrhœal stomatitis.

The existence of gonorrhœa buccalis has further been established by the occurrence of primary urethral infections after coitus "ab ore" with prostitutes.

Chantemesse (1891) published the case of a foreigner who developed, ten days after perverted coitus in this manner, a urethral discharge which contained a great number of gonococci.

Von Geissler (1908) described a similar case, where the urethritis occurred four days after coitus "ab ore." This patient had never had gonorrhœa previously.

Luys (1917) reports a case of urethral infection from an "ab ore" coitus in one of his patients. It occurred in a young man who had copulated in this perverted manner with a prostitute. He was about to get married in a few days, and considered that by copulation in this manner he would not risk getting a gonococcal infection. Four days later, however, he developed a profuse discharge in which numerous typical gonococci were found.

Luys states that in cases of this kind the gonococci are often deposited in the mouth, which receives them for the moment without showing any reaction, and the infective material can be taken over by a second individual who is addicted to the same vice.

Mayhew (1918) describes a case of oral gonorrhœa, with photographic illustrations. The patient was a student of 19, who was infected after visiting a dentist in order to have his teeth cleaned. The whole picture presented a most severe type of mouth infection, with swollen submaxillary glands and a temperature of 100.2° F. Smears from the pus showed intra- and extracellular Gram-negative biscuit-shaped diplococci. This organism grew slowly on glycerine-glucose agar containing ascitic fluid, hydrocele fluid, or blood serum, but it would not grow on plain agar. He believed that the organism was the gonococcus, and excluded the meningococcus and the *M. catarrhalis*.

Nasal Gonorrhœa is even more rare than an oral infection, in spite of the fact that, being close to the eye, the nose is sometimes more or less exposed to infection.

Several authors have reported cases of gonorrhœal infection of the nasal mucous

membrane, but most of these lacked definite bacteriological proof, and several experiments have been unable to show that the gonococcus is capable of infecting this part of the body. Thus Diday failed on several occasions to produce a nasal gonorrhœa by rubbing the septum with a finger contaminated with gonorrhœal pus. Bonnière likewise failed to produce an infection by painting the pituitary mucous membrane with a brush which had been dipped into the pus from a case of gonorrhœal ophthalmia.

Nevertheless, Andrew Duncan described a case of what he considered to be nasal gonorrhœa, which occurred in a young man who had wiped his nose with a towel which was soiled with pus from his urethra. A special type of coryza supervened, but its nature was not proved by bacteriological examination.

According to Jullien, certain cases of coryza in infants, which occur on the second or third day after birth, are of gonococcal origin, and he considered that the nose in these cases was infected at birth by the gonococci present in the genital tract of the mother.

Gonorrhœal Infection of the Ear.—Reinhard (1907) described a case of gonococcal otitis, but this condition is certainly an extreme rarity.

Putzig (1919) cites a case of purulent otitis media in a fourteen-months-old child which occurred nearly two months after the child had been successfully treated for a typical gonorrhœa. He thinks the ear condition was due to a second infection transmitted from the mother, who was still suffering from a gonorrhœal discharge. He emphasises the need of a bacteriological examination of the discharge in all cases of persistent suppuration of the ear in infants, especially those who have had a gonococcal infection. One per cent protargol and potassium permanganate lavages usually cure the condition in a few days.

Direct Skin Infections.—Meyer (1903) reported on the case of a patient who suffered from a profuse vaginal discharge containing gonococci, and who developed a superficial whitlow on her right middle finger a few days after she had scratched it. A big, slightly raised bleb, containing a yellowish fluid, made its appearance on the outer surface of the finger, which was incised. The pus withdrawn from it contained gonococci, as proved by microscopic examination and cultural proof.

Froget (1906) reported on a case of gonococcic inflammation of the scalp in an infant ten months old suffering from gonorrhœal urethritis. Redness, swelling, and induration developed over the posterior aspect of the cranium in patches. Two small papules appeared in one of the indurated patches, and later became pustules. The pus from the latter showed numerous intracellular gonococci. The gonococcus was also found in the urethral discharge. This author states that gonococcal inflammation of the cellular tissues resolves very rapidly.

Wright (1909) described a case of pustular folliculitis involving the bearded part of the face. The condition had existed for two years, and resembled an ordinary sycosis. The roots of the hairs, when examined microscopically, showed large numbers of extra- and intracellular diplococci identical with the gonococcus (he does not state what stain was used). He states that in Pusey's work there is a reference to a report by Cronquist of a case of gonococcal folliculitis of the hairy region of the abdomen of a woman who had gonorrhœa. Wright considers that his case of sycosis was probably due to the gonococcus, and states that the barber had been under treatment for gonorrhœa at the time of the patient's infection.

Nylander (1909) described two cases of gonorrhœal serpiginous ulceration occurring in men.

Hurst (1910) reported on a case of gonorrhœal skin infection in a man aged thirty-six. A week after having his hair cut in a barber's shop, he developed a papule in the temporal region where he had had a scratch. Microscopic examination showed pus with intracellular Gram-negative diplococci as well as staphylococci. The culture showed typical colonies of gonococci. The patient had no urethral infection. He also described another case in a boy who developed a gonorrhœal infection below the angle of the lower

lip. Pus from the lesion showed typical gonococci. The infection was traced to a camp towel, used by another boy suffering from a urethral discharge.

Anwyl Davies (1919) reported on a case of gonorrhœa in a girl of nineteen years with a copious vaginal discharge. There was also an abundant yellow discharge from the umbilicus. Gonococci were found in both discharges. The umbilical discharge persisted in spite of treatment, and a pedunculated papilloma developed to the size of a small walnut, like a large gonorrhœal wart. During the week before removal, it became very soft and spongy, and exuded a profuse yellow discharge. Papillomata likewise developed on the vulva and on the perineum. Caustics and astringents were of little value. Hence it was excised, after which it healed rapidly.

The author would like to draw attention here to a very extraordinary case which came into Dr. Allport's clinic at the Military Hospital, Rochester Row. (See photograph No. 1, Plate XVIII., in the next chapter.) This patient showed no trace of urethral gonorrhœa, but in the skin on the lower surface of his penis were three purulent nodules, clearly shown on the photograph. The pus from these showed numerous intracellular gonococci, and the germ was grown in pure culture on glucose-plasma agar. It would appear that this was a case where the patient was infected on the outside of his penis and where the urethra escaped infection completely. The pustules were incised and treated with an antiseptic, and they disappeared very quickly.

Gonococcal Ophthalmia or Exogenous Gonococcal Conjunctivitis.—As already mentioned, the mucous membrane of the eye is much more susceptible to gonorrhœa in childhood than in adult life. This affection is very common in infants (*Ophthalmia neonatorum*) whose mothers are suffering from gonorrhœal vaginitis. The contamination usually takes place at birth, whilst the head of the infant passes through the vagina. The inflammation of the conjunctiva supervenes on the second or third day after birth. An incubation period of four or five days is very rare, and an interval of six or seven days is quite exceptional. When the conjunctivitis is congenital, the infection, according to Péchin (1917), has taken place *ante partum, in utero*; the membranes ruptured prematurely, and the gonorrhœal secretions of the mother's vagina found their way into the amniotic sac.

The infection of the conjunctiva is characterised by a more or less free amount of discharge and a variable degree of swelling of the eyelids. Intense suppuration is very common, but there are benign forms with slight symptoms. The symptoms are usually severe, and the disease takes a rapid and destructive course. Perforation, and even panophthalmia, supervene in spite of all treatment.

The most frequent complication of gonococcal conjunctivitis is an infection of the cornea, which may lead to ulceration, perforation, retro-choroidal hæmorrhage, lesions of the iris, secondary glaucoma, leucoma, staphyloma, panophthalmia, and anterior polar cataract.

The best prophylaxis against ophthalmia neonatorum consists in putting a few drops of silver nitrate solution into the conjunctival sac immediately after birth.

Diamare (1919) noted that out of 140 cases of gonococcus ophthalmia, the severest lesions were always those with the gonococcus in pure culture. When it was associated with the *Koch-Weeks* bacillus the course was exceptionally mild and the ophthalmia healed harmlessly. He suggests the feasibility of using the virus of the Koch-Weeks bacillus to attenuate the gravity of a pure gonococcus ophthalmia. For information on gonococcal metastatic or endogenous affections of the eye, see next chapter.

The Female Organs liable to be Infected.—Genital gonorrhœa in the female is liable to be much more complex than in the male. Thus it may spread from the urethra, vulva, and vagina to the cervix, to the uterus, and to the Fallopian tubes and ovaries. These complications do not arise through the blood stream, but by direct spreading of the infection up the genital tract.

In man, the compressor urethræ muscle tends to act as a slight barrier to the upward

progress of a gonococcal infection. So in women the germs may be unable at first to get beyond the internal os uteri. Sooner or later, however, during the menstrual periods, during sexual excesses, or during the puerperium, the infection is liable to gain an entrance into the cavity of the uterus itself. In this locality the germs are able to penetrate below the mucous membrane to the muscular layers, thereby producing metritis and para-metritis. Later the organisms succeed in spreading through the external orifice of the Fallopian tubes to the tubal mucous membrane. In such cases there is produced as a rule a certain amount of pus which often develops into a definite abscess. By the escape of this pus through the ostium abdominale a peritonitis may result. So also the ovaries may be attacked, producing an ovaritis.

Gonorrhœal Urethritis in Women.—As already stated, the female urethra is very susceptible to infection. As in the case of the male, this mucous passage becomes red and congested, and a certain amount of pus is discharged. By pressing on the lower wall of the urethra from the vagina a considerable amount of pus can, as a rule, be squeezed out of the meatus.

Micturition is usually painful and scalding. Cystitis often occurs, and this is characterised by frequent desire to urinate. The acute stage of urethritis in the female may be very short and mild, and may, in fact, be scarcely noticed by the patient. The only certain mode of diagnosis is the finding of gonococci by microscopic examination of the discharge. A few drops of pus can usually be obtained by introducing the finger into the vagina and pressing from behind forwards, so that the urethra is compressed against the posterior surface of the pubis.

As in the case of the male, pus is most likely to be obtained some hours after the last urination; for example, before micturition in the morning.

Gonorrhœal urethritis in the female may become chronic, and results in a proliferation of the epithelium, giving rise to the formation of small polypi. Moreover, strictures may arise due to proliferation and fibrosis of the submucous layers. As in the case of the male, the urethral mucosa of the female has numerous diverticula and small glands corresponding to the Littre's follicles. There are a large number of follicular glands arranged in two lateral groups near the meatus (Hamonic, 1910). All of these glands are liable to become infected, and a peri-urethritis results. Further, there are numbers of small glands around the orifice of the meatus, and these are frequently infected, producing a *para-urethral folliculitis*. This condition is characterised by small inflamed raised spots around the meatal orifice. Pus can usually be expressed from these red and swollen follicles, and frequently it will be observed by exploring with a stylet that small fistulae are connected with them. This infection of the para-urethral follicles, and the concomitant fistulae, are often very persistent and difficult to cure. As a further development of this condition, small abscesses are apt to develop in the vestibule, which may burrow into the tissues and cause considerable trouble.

The treatment is more or less identical with that used in urethritis in the male—irrigation, dilatation, etc. As in man, the condition is often very persistent and difficult to eradicate.

Gonorrhœal Vaginitis.—The vagina, as already mentioned, is more readily infected in infants than in adults. The signs and symptoms are quite definite, since, as a rule, there is a profuse discharge of pus from the vagina, and there is considerable pain and discomfort in walking.

According to Verchère (1894), the upper portion of the posterior wall and the posterior fornix are most commonly affected, whilst the anterior fornix is rarely implicated. This is supposed to be due to the anatomical relations, since if the cervix and uterus are infected the discharge falls back into the posterior fornix. Further, during copulation the penis is also directed towards this portion of the vagina.

Verchère described three types of vaginitis as noted clinically :—

Congestive vaginitis, where at first the mucous membrane is red, smooth, and glistening,

and covered with pus. Later there is marked proliferation and desquamation of the lining epithelium, which forms an adherent caseous and fetid coating over the mucosa.

Granular vaginitis.—In this condition the mucous membrane is studded over with more or less extensive granulations, so that it has an irregular, granular, roughened appearance.

Diphtheroid vaginitis, which is less common, is characterised by a thick yellowish-white lardaceous coating which adheres firmly to the vaginal wall. It would appear that this diphtheritic condition of the vagina may be due sometimes to germs other than the gonococcus.

Kobrak (1914) described two non-gonococcal cases in little girls of nine years of age, wherein the condition simulated gonorrhœa. The vagina in both these cases showed a whitish appearance exactly like the throat in diphtheria, but there was no membrane. Smears showed true diphtheria bacilli, and the condition cleared up under anti-diphtheritic serum.

The author has noted that practically all vaginal discharges in gonorrhœa show an enormous mixed infection of germs composed of staphylococci, pneumococci, diphtheroids, *Bacillus coli*, Gram-negative diplobacilli, etc. Indeed, the secondary organisms are as a rule so numerous that one can only detect the gonococcus with great difficulty amongst them. In such cases one has often to rely upon the complement-fixation test for diagnosis.

Treatment.—Numerous forms of treatment have been recommended for gonorrhœal vaginitis, such as antiseptic douches, also tampons impregnated with iodoform, salol, glycerine, etc. These tampons keep the inflamed surfaces of the passage apart.

Watson (1910) obtained good results by introducing lactic acid fluid, containing the lactic acid bacillus, into the vagina, and also had excellent results in the male in two cases with such treatment. This idea arose from the fact that the vaginal secretion is normally acid on account of the presence of the vaginal bacillus, and it is supposed that this natural acid content helps to keep the gonococcus and other germs in abeyance.

In the author's experience the secretion from the healthy vagina normally contains only a few epithelial cells with numerous vaginal bacilli and few other organisms. When, however, the passage becomes unhealthy, the secretion shows pus cells, enormous masses of organisms of many kinds, and in these cases the vaginal bacilli are often scarce or absent.

Taussig (1914) tried the lactic-acid bacillus treatment, but obtained little benefit from it.

The author on one occasion made a culture from a lactic-acid pessary, and was unable to obtain any growth of this bacillus from it. In trying this form of treatment, therefore, one should make certain that the pessary containing the supposed germ is really active.

Gonorrhœal Cervicitis and Metritis.—According to Wertheim and Bumm, the gonococcus may remain for a long time in the cervix and uterus after it has disappeared from the vagina. The cervix uteri is much more commonly affected, however, than the actual body of the womb itself.

According to the statistics of Heiman (1895 and 1896), the cervix was involved in 138 out of 237 cases of genital gonorrhœa in women.

Marschalko (1900) found that out of 161 cases the uterus was infected in 108. In chronic gonorrhœa, according to this observer, the disease was found to have spread to the os uteri in at least 50 per cent to 64 per cent of the cases.

Eberhard (1904) gave similar figures compiled from the statistics of his own clinic.

Bumm treated 74 gonorrhœal women from the commencement of their infection until they were cured. The average duration of the disease was five months, and some lasted two years. Cervical gonorrhœa developed in 70 per cent of these cases.

According to Luys (1917), the cervix of the uterus is much more often attacked than the body. The onset of gonorrhœal cervicitis is often acute, and is ushered in by pain in the supra-pubic region or in the loins, and by a copious discharge.

On examination with the speculum, the mucosa of the cervix is found to be puffy;

its lips are everted and swollen; the circumference of the os is studded with small raised patches and little ulcers. Sometimes these excoriations coalesce and form one large ulcerated surface. The chronic form, however, is much more common. The symptoms are not characteristic. Menstruation generally becomes more painful and troublesome. It is irregular, and tends to commence too early and lasts longer. There is a more or less marked leucorrhœa, and the cervix is found to be enlarged and swollen.

Gonorrhœal Endometritis.—According to Bumm, 23 per cent of all gonorrhœal females develop endometritis. The condition generally arises as a direct extension of the disease from the cervix to the body of the uterus. The condition nearly always becomes chronic. The uterus is found on bimanual palpation to be enlarged and painful, and a persistent purulent discharge comes from the cervix, which is also swollen and congested.

Wertheim demonstrated that the gonococcus spread from the uterine mucosa to the parametrium by way of the lymph channels, and that the germ could give rise to inflammatory troubles in that tissue.

The symptoms produced are usually general malaise, fever, loss of appetite, also vague diffuse pains in the lower abdomen, which may radiate to the loins.

The prognosis should be guarded because of the complications which are liable to supervene, such as salpingitis, cellulitis, etc. The treatment consists of douching, etc. Cupping the cervix, which aspirates the pus and slime from the cavity of the uterus, is very useful.

Apart from the general treatment consisting of rest in bed, hot douches, etc., the condition should also be treated by local measures. Good results have been obtained by dilatation of the cervix, and by application of solutions of silver nitrate, zinc chloride, iodised phenol, etc., to the uterine mucosa.

Luys states that intra-uterine irrigations, such as with potassium permanganate, should be avoided, as they may force the infection upwards towards the Fallopian tubes. Intra-uterine cauterisations have been used by several authorities. Thus solid caustics have been applied by introducing a stick of silver nitrate into the uterine cavity, or liquids such as zinc chloride, weak nitric acid, or phenol may be applied on swabs.

These liquid substances have also been used by the instillation method, by means of a Braun's intra-uterine syringe. About 3 c.c. of the chemical is introduced, and good results have been obtained by this method, which as a rule is very painful.

The uterine cavity may be massaged by insufflations of hot air; and, finally, curative results have been obtained by electrolysis, and also by curetting.

Gonorrhœal Salpingitis and Ovaritis.—Marschalko (1900) estimated that the tubes and ovaries became infected in about 41 per cent to 49 per cent of all cases of chronic gonorrhœa in females.

Bumm, on the other hand, estimated the figure at 10 per cent. It is the frequent occurrence of these complications that renders gonorrhœa of such importance in women. Nöggerath (1872) was probably the first to teach that this disease often affected the whole genital tract in the female; and for definite bacteriological proof of the ætiologic importance of the gonococcus in the inflammatory diseases of the inner genital organs in women, we are indebted before all to the works of Bumm and Wertheim.

We now know with certainty from the researches of Kossman (1900), Metzner, Muscatello, and others, that the gonococcus alone can produce purulent inflammation of the tubes and ovaries, and that the disease can spread to the peritoneum. Nevertheless, it is also definitely established that quite frequently the original gonococcal infection can be complicated by infections with secondary organisms, chiefly staphylococci and streptococci. These mixed infections vary the clinical characters of the disease in manifold ways. According to Luys (1917), gonorrhœal salpingitis is usually insidious in its onset. In most cases the woman is perfectly unaware of her illness, and only realises the nature of her complaint after she has consulted her doctor.

Diagnosis.—Bimanual examination shows the ovary to be enlarged and displaced.

As a rule, it has moved towards the uterus or dropped into the pouch of Douglas. The tube is felt as a thick, well-defined cord running outwards from the uterus towards the brim of the pelvis.

The functional troubles are chiefly menstrual, such as amenorrhœa, dysmenorrhœa, or great pain during menstruation.

The complement-fixation test is of great value in the diagnosis of these adnexal inflammations, since gonococcal affections of the tubes and ovaries always give a strongly positive reaction. Indeed, if the reaction is negative it may be taken as almost certain that the condition is not gonococcal in nature.

Miller (1912) contributed a paper on the histological differentiation of gonorrhœal salpingitis, and de Bovis (1912) wrote an article describing the rôle of the gonococcus in the origin of pyosalpinx. The literature on the subject is very large.

Treatment.—In cases of salpingo-ovaritis it is essential to treat the metritis, just as in man it is necessary to treat the posterior urethra in cases of epididymitis. Vaccine treatment is often of very great value in these cases, and should always be tried before resorting to surgical operations. If, however, all treatments fail, it may be necessary to operate, but it is better to wait until the acute inflammatory symptoms have subsided.

Van de Velde (1912) found that old inflamed ovaries or tubes swell and grow more tender during the negative phase after an injection of gonococcal vaccine. Such a dose of vaccine may be of diagnostic as well as of curative value. For further information on the vaccine and serum therapy of these conditions see Chapters XXX. to XXXIII.

Gonococcal Peritonitis.—The excellent researches of Wertheim (1891) have shown that a gonococcal infection of the Fallopian tubes is not always confined to the mucous membrane. Frequently the germs proliferate completely through the walls of the tubes and reach the peritoneal covering. When an abscess develops in the ovary, the peritoneal covering of that organ may also become affected. Although such cases of peritonitis are truly gonorrhœal in nature, yet it has been proved that the gonococcus finds the peritoneum a more or less unsuitable nidus for its growth and development. In consequence, a true gonococcal peritonitis, as a rule, does not spread, but is limited and rapidly healed by adhesions and thickenings. Rousseau believed that acute and fatal peritonitis cases were always due to mixed infection.

Battez (1902) collected 30 cases of gonococcal pelvic peritonitis in the male, following upon infection of the bladder, prostate, and seminal vesicles.

Dudgeon and Sargent (1905) described 4 cases of gonorrhœal peritonitis spreading from a pyosalpinx. The onset was sudden, but the progress of the symptoms was not very acute. In 2 cases they found intracellular diplococci in films. They concluded that the gonococcus causes a peritonitis which may be diffuse or localised. The onset may be sudden, but the subsequent symptoms are those of a low form of peritonitis. The prognosis is in their opinion favourable.

Foulerton (1905) described a case in which gonococci were found by the microscope and by culture in the peritoneal exudate. They were also found in the pus of both tubes, and in the vaginal discharge. He believed that the peritoneal infection in this case was due to an acute kink in the middle of the right tube. The tubes were removed by operation.

Albrecht (1912) gave particulars of 4 cases of diffuse gonorrhœal peritonitis. In 2, operative treatment was applied. In every case the peritonitis developed with a stormy onset, but the symptoms subsided rapidly. The mild character of gonorrhœal peritonitis is confirmed by these experiences.

Luys (1917) states that in the acute forms of gonococcal peritonitis, which are rare, the patient suddenly feels violent pains in her abdomen, accompanied by tympanitis, vomiting, high fever, rapid pulse, with paralysis of the bowels, prostration, and the characteristic pinched, anxious face. The chronic form is much more frequent, and gives rise to characteristic findings on bimanual examination. Behind the uterus one feels a hard,

resistant, very painful and doughy mass. Cases of this kind should also be explored *per rectum*, as very often valuable diagnostic information can be gained in this way.

He states further that gonococcal peritonitis is characterised by its irregular course, in which exacerbations of variable intensity and remissions alternate, and its duration is almost unlimited. Hence quite a number of women suffering from these affections have to pass a great part of their existence on a sofa.

Salcedo (1919) states that gonococcal peritonitis in onset is the same as any other diffuse peritonitis, but the general condition keeps more favourable. There is not so much vomiting and tympanism, and the septicæmia seems to be mild. Laparotomy shows that the primary focus is in the tubes or ovaries, or both. The secretions do not have the usual faecal odour. He advocates operating at once. In one fatal case the gonococcus and streptococcus were associated, and the toxæmia was intense.

Wildenskov (1920) reports the eleventh case of gonococcal peritonitis at a Danish public hospital. All cases were women, and he calls attention to the arrest of menstruation as an early symptom. Tenderness in both iliac fossæ, early meteorism, and lack of stiffening of the abdominal wall are also instructive in the diagnosis of the toxic form, and even with the infectious form the prognosis is more favourable than peritonitis of other origin. The mortality was only 16·6 per cent in the 36 operative cases on record. He adds: "Expectant treatment at first; but if the conditions grow worse instead of better, operate at once."

Treatment.—Just as in the case of salpingitis, it is wise to treat gonorrhœa in the uterus and elsewhere. In the acute stage the patient must have complete rest in bed, with copious or frequent hot douches. Ice-bags applied to the abdomen often relieve the pain.

Luys recommends that an operation should be performed, and that the appendages should be removed as soon as the condition of the patient is suitable for surgical interference.

Since, however, gonococcal peritonitis is not likely to end fatally, the author thinks that it would be advisable to give a thorough course of vaccine therapy before resorting to such a drastic surgical operation, whereby the woman is permanently sterilised.

Gonorrhœal Bartholinitis.—According to Luys (1917), this condition is usually unilateral, and occurs perhaps most frequently on the left side. The condition is shown by the appearance of a swelling on the side of the vulva. This swelling is of variable size, directed from above downwards, and covered by a tense, red, smooth, and swollen mucous membrane. The inflamed gland can easily be palpated between two fingers. If the duct is patent, greenish-yellow and often foetid pus can be made to escape from it by pressure on the gland. When the acute stage has passed, the condition is liable to remain for a long time in a chronic form, and is one of the most tenacious and commonest localisations of gonorrhœal infection in women.

The duct may become occluded, and an abscess may form, which gradually burrows to the surface, producing a fistula or sinus of variable length, which is usually sinuous.

Although a Bartholinitis may subside into apparent quiescence, nevertheless it may harbour gonococci and remain a source of reinfection to the patient herself, as well as to others. In this chronic latent inflammatory condition the gland is painless, and may be no larger than a cherry-stone. It can be detected, however, by palpating the labium majus and minus between the thumb and the forefinger.

Luys maintains that a chronic Bartholinitis in woman is of the same importance as a chronic littritis in man. Thus Bartholin's glands often harbour the gonococcus for a considerable time, and they are apt to give rise to sudden recrudescences after long intervals—many months, and even years. These glands should therefore always be examined, and treated if necessary.

Colombini (1899) gave an account of his bacteriological and histological researches on this complication of gonorrhœa.

Treatment.—In the acute stages, hot baths and hot injections. Once an abscess has formed, the pus should be evacuated by incision. The only satisfactory method, however, of eradicating the disease is complete excision of the gland.

Gonorrhœa in Children.—**Vulvo-vaginitis.**—This condition is by no means rare, and sometimes occurs in epidemic form, especially in institutions for female children of the poorer classes.

Suchard (1877) recorded an epidemic of vulvo-vaginitis which broke out in Lavey. Several little girls were infected. The epidemic lasted twelve to fifteen days, and was only stopped after the common swimming-bath had been disinfected. Cases of direct infection also occur due to precocious sexual intercourse, and are met with more commonly amongst the negro races.

De Minine (1895) described many cases due to direct sexual infection amongst black children, living in a state of nudity.

Prat (1912) pointed out that the disease may be contracted in this fashion even in Europe, but this is comparatively rare.

Veil and Bayon (1904) described an epidemic of vulvo-vaginitis in which the infection had been carried by a thermometer.

Alice Hamilton (1908) states that infantile gonorrhœal vulvo-vaginitis is usually carried through the medium of baths, rectal thermometers, bed linen, diapers, night clothes, closet towels, sponges, the fingers, etc. The condition is very persistent and difficult to cure, and often spreads upwards.

Bendig (1909) described two epidemics of the malady which occurred in two institutions for girls of the poor classes. Thus out of 40 girls between seven to ten years of age, 15 contracted vulvo-vaginitis from one girl aged eight years. The infection was found to have been transmitted by the custom of bathing two girls at once in the same water and drying them with the same towel.

Louise Morrow and Olga Bridgman (1912) found that 55 per cent of 200 female children admitted annually to a state training school had gonorrhœa on admission.

In certain cases, of course, the disease is caused in little girls who have been raped by adult gonorrhœal subjects. More often, however, they are infected by their parents, especially amongst the very poor, where the parents are in the habit of taking their children into their own bed even when they are suffering from gonorrhœa. In such circumstances, accidental infection from bed-clothes, etc., is by no means uncommon.

In contrast to the infection of adult women, chronic gonorrhœa in little girls has little tendency to spread beyond the cervix. This is probably due to the fact that in children the cervix is more or less sealed up. Nevertheless, cases have been published by Gassmann (1901), Buschke (1902), and Jung (1904) where the infection spreads further afield; and other cases where peritonitis actually supervened have been described by Hunner and Harris (1902), Galvagno (1904), Baer (1904), Welt-Kakels (1904), and Variot and Sebilleau (1904). Galvagno recorded a mortality of 20 per cent in the cases of infantile gonococcal peritonitis which came to his notice.

With regard to the *curability and prognosis* of infantile vulvo-vaginitis, many papers have been written; *vide* Rubin and Leopold (1913), Spaulding (1913), G. G. Smith (1913, 1914), etc. Smith states that it is very difficult to state when the disease is cured, since negative smear examinations are very inconclusive. Considerable success, however, was obtained by the complement-fixation test, and it was shown that in some cases the disease could continue for three or four years. Pontoppidan (1915) collected statistics in 779 cases of gonococcal vulvo-vaginitis in little girls who had been treated at a Copenhagen hospital since 1896. He found that complications were recorded in 6.8 per cent. He re-examined 22 per cent of the cases since 1907. In 8 of the 79 patients gonococci had still been present when the girls had been discharged from the hospital, but a recurrence was known in only two instances. All the others seemed to be clinically cured. The treatment used was the local application of silver nitrate and other silver salts, in concen-

trations varying with the age of the child. In his experience the infection occurred usually about the age of two years, and several months' treatment was required. In certain cases, exacerbations and remissions kept up for several years, but the final result seemed to be a complete cure, so that there was little, if any, danger of the disease dragging along into adult life (see also Chapter XVII. p. 150 and Chapter XLVII.).

Clinical Signs and Symptoms.—According to Luys (1917), the infection may escape notice for a time, but sooner or later a profuse vaginal discharge comes on which soils the linen. The vulva is in a state of redness, which is accompanied by irritation, and often by intense erythema. The acute symptoms soon subside, but the condition may go on in a chronic state for a very long time. In fact, the grave character of this disease lies in its long duration and its often exasperating rebelliousness against treatment. Complications, such as cystitis and arthritis, may occur, but are exceptional.

Treatment.—Many authors have found good results from vaccines (see Chapter XXX. on Vaccine Therapy).

Luys recommends irrigations with 1 in 8000 potassium permanganate, whilst others have obtained success with more or less strong applications of silver nitrate and other silver salts.

Gonorrhœa in little Boys.—This is less common than vulvo-vaginitis in little girls.

Wolbarst (1910) observed personally 37 boys between the ages of sixteen months and fourteen years who were suffering from gonorrhœa. The greatest incidence of the infection was between four and ten years, and the diagnosis was established by microscopic examination. The causes of the infection are more or less the same as in the case of vulvo-vaginitis in little girls, soiled linen, bed-clothes, etc., also the wearing of the old discarded clothes of gonorrhœal adults. Wolbarst witnessed the case of a little boy who was infected in hospital by having a dirty catheter passed.

Chaumier (1909) collected 11 cases wherein the boys were infected through the sexual perversity of maids and governesses.

The disease in boys takes the same course and has the same complications as in adults. Retention and strictures may occur.

According to Luys (1917), purulent ophthalmia is a common complication. Cystitis has also been observed, but so far only one case of epididymitis has been recorded, viz. the case of Reinhard (1914). The infant in question was infected at birth, and developed a urethritis, which subsided and was followed by an attack of epididymitis. Subsequently the left knee was implicated, and finally death occurred from gonorrhœal septicæmia. The mother had been treated for gonorrhœa, and her disease was supposed to be "latent" at the time of birth.

General gonococcal infections have been recorded in male children. Thus Nicoll and Wilson (1913) described a case in a boy of 2½ years. The gonococcus was obtained in smears and cultures from the urethral discharge. There was an indefinite history of fever three weeks previously. The left elbow and knee became swollen and very tender. The right sterno-clavicular joint became swollen and developed an abscess. This was evacuated, and gonococci were found in the pus. Later the left shoulder became similarly swollen and painful, pus was evacuated and found to contain gonococci. The complement-fixation test was positive. Vaccines were administered, and the child eventually recovered. Wolbarst met with a case complicated with arthritis, in which cachexia and death supervened.

The *treatment* of gonorrhœa in young boys is the same as in the case of adults. Luys points out that special attention should be given to the prepuce, as most boys have a certain degree of phimosis. If necessary, circumcision should be performed in order to prevent a paraphimosis.

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CHAPTER XXIII

GENERAL OR SYSTEMIC GONORRHOÆAL INFECTIONS. METASTATIC AND TOXIC MANIFESTATIONS

SEPTICÆMIA—PYÆMIA—METASTATIC ABSCESSSES—ENDOCARDITIS—MYOCARDITIS—PERICARDITIS—PLEURISY—PNEUMONIA—PHLEBITIS AND ARTERIAL THROMBOSIS—AFFECTIONS OF THE BONES—ARTHRITIS—RHEUMATISM—MYOSITIS—BURSITIS—SYNOVITIS—AFFECTIONS OF NERVOUS SYSTEM—AFFECTIONS OF SKIN—METASTATIC NEPHRITIS—AFFECTIONS OF CONJUNCTIVA, CORNEA, IRIS, CHORIOID, OPTIC NERVE.

ALTHOUGH the gonococcus attacks in the first place the mucous membranes of the genital tract and only occasionally penetrates further than the submucous connective tissues, yet it can also in exceptional cases pass into the system by way of the lymphatics and capillaries, and penetrate to the most remote parts of the body.

When this occurs we have what is known as a metastatic gonococcal infection, and the germ may then be classed in the same category as the staphylococcus and those other organisms which are capable of giving rise to septicæmia and pyæmia.

It has been definitely proved that the gonococcus can pass from the mucous membrane along the lymphatics, since the germ has been cultivated from purulent inguinal and cervical glands in the male and female respectively; *vide* Colombini (1898–1900), Mysing (1900), and Hocheisen (1906). The presence of the germ in the blood stream has also been demonstrated in numerous cases of general gonococcal infection.

Bouchard and Capitan (1878) were the first to find gonococci in the blood. Later they were also found by Petroni (1883) and Jullien (1896). Eventually, when the technique of growing the germ was greatly improved, its presence in the blood was frequently demonstrated by culture methods; *vide* Thayer and Blumer (1896), Ahmann (1897), Colombini (1898), Thayer and Lazear (1899), Unger (1901), Barbiani (1902), Markheim (1902), Diggelmann (1902), Reye (1903), and Nobl (1903).

Bressel (1903), in a case of pneumonia supervening on the decline of a gonorrhœa, obtained a pure culture of gonococci from the blood on the fourth day, but failed later to isolate the germ.

In 1905–1906 the germ was successfully cultivated from the blood by Krause, Wynn, Prochaska, Duval and Lewis, Widal, Thayer, Horder and Faure-Beaulieu. The latter observer collected 34 instances in which the gonococcus was grown from the blood, and Dieulafoy (1909) collected 37 cases in which successful blood cultures were made. Rueck (1913) also grew the germ from the blood in cases showing complications of gonorrhœa.

Irons (1910) described the following six cases of gonococciæmia in which he isolated the gonococcus from the blood by culture during life.

Case 1.—Exceedingly chronic type of gonorrhœa of ten years' standing with relapses or re-infections, also hydrocele and recurring arthritis. During the attacks there was continued fever with relatively slight remissions, together with abdominal maculo-papules, some of which could not be distinguished from the rose spots of typhoid fever. Vaccine was given, and the temperature fell gradually and improvement in the joints followed.

Case 2.—History of eight months' illness with gradually increasing palpitation, dyspnoea, irregular fever and chill, progressive aortic valve murmur, enlarged spleen. This case was diagnosed as gonococcal ulcerative endocarditis of the aortic valve, since gonococci were isolated in pure culture from the blood. The leucocyte counts were lower than those usually found in gonococcus infections.

Case 3.—Fever, 101-103° F., later 105° F., and death. Multiple arthritis.

Case 4.—Fever, dyspnoea, joint symptoms, cardiac murmurs, no doubt due to ulcerative endocarditis. Condition occurred one week after the onset of the gonorrhoea.

Case 5.—Fever and sudden development of multiple arthritis. Abdomen and chest showed a number of small, slightly raised reddish maculo-papules which partially faded on pressure. Leucocytes 21,000 per c.mm. Gonococci 2-3 colonies per c.c. of blood. Apart from the finding of gonococci in the blood, the symptoms were like typhoid. The patient had chronic urethritis.

Case 6.—The gonococci were isolated from the blood during an acute exacerbation of gonococcal arthritis. There was no evidence during the entire course of the illness of any endocardial lesion.

Lafaro (1911) stated that in ordinary acute cases of gonococcal urethritis, blood cultures were always negative. In chronic cases of urethritis, however, especially those complicated with stricture or epididymitis, the blood cultures were mostly positive.

Lenhartz (1897) cultivated gonococci from the spleen in a case of gonococcal septicaemia.

The gonococcus, like other pyogenic organisms, when it once enters the blood stream settles down on certain predisposed parts. The special localities favoured are the synovial membranes of the joints and tendon sheaths, the valves of the heart, more rarely the serous membranes, and the subcutaneous cellular tissues. The disease in these places resembles more or less the conditions produced by the other pyogenic organisms. Thus in the joints one finds serous or purulent effusions. On the valves of the heart warty vegetations are produced, more rarely ulceration. Infection of the subcutaneous cellular tissues, on the other hand, results in abscesses containing pus or hæmo-purulent matter. It will be seen, therefore, that gonorrhoea is not always merely a local infection. At any moment it may become a septicaemia which may prove rapidly fatal, or it may induce acute or chronic joint disease, ulcerative and proliferating endocarditis, pericarditis, broncho-pneumonia, infarcts in the lungs or other organs, peritonitis, pleurisy, phlebitis, periostitis, iritis, chorioiditis, meningitis, neuritis, myositis, etc. Each of these conditions will be considered in detail later.

Hamilton (1902) pointed out that systemic or metastatic gonococcal infections were more common in the male than in the female. This he considered was due to the greater resistance offered by the uterus and pelvic peritoneum in the latter to the spread of the infection.

Wynn (1905) believes that the greater incidence in the male is due to the greater length of the male urethra with its numerous diverticula, glands and sinuses.

Kreissl (1912) stated that systemic gonorrhoea was more common in men than in women, because probably the latter are less liable to traumatic injury of the urethra or vagina. It required, in his opinion, either local retention with subsequent trauma of some sort, or an abrasion of the protecting epithelium, in order to allow the escape of the gonococci or their toxins into the blood-vessels or lymphatics. The trauma may be due to instruments, or to invasion of the neck of the bladder and the trigone by the gonorrhoeal process, leading to congestion and bleeding and exposure of the smaller capillaries. Congestion due to sexual excitement increases the chances of trauma. He points out that a systemic infection such as arthritis seldom occurs in the early stages of gonorrhoea. A few cases of gonococcal pyæmia have been recorded in which the condition appeared within a few days after the first urethral infection. This he considered may have been due to idiosyncrasy, or it may have been due to lesions such as mentioned

above. Such lesions may be caused by irrigation under too great a pressure. He states that the idea is gaining ground that the source of systemic infection in the male is any retention focus in the uro-genital tract from the anterior urethra up to the renal pelvis. Such foci occur in the follicular glands of the anterior urethra, in the glandular tissues of the prostate, in the Cowper's glands, and in the seminal vesicles. Very few have appreciated the importance of the seminal vesicles as a contributing factor in systemic infection. Retention of septic material in the seminal vesicles, according to this author, is responsible for a very large proportion of chronic ever-recurring urethral discharges, relapses of epididymitis and cystitis, and metastasis in the joints and other tissues. Comma-shaped shreds originate in the prostatic follicles and in the seminal ducts, from which they are expelled by the terminal contractions of the circular muscle fibres. The recent term "crypto-genetic" sepsis owes its origin largely to these retention foci in the seminal vesicles and the other appendages of the uro-genital tract. There are cases in which Nature succeeds in building a wall around these foci by a peri-vesiculitis, enclosing the germs, which subsequently die out.

Zieler (1912) maintains that anything which tends to aggravate an acute gonorrhoeal catarrh such as trauma, excesses of any kind, menstruation and pregnancy, favours the irruption of the germs into the blood.

Gonococcal Septicæmia.—Faure-Beaulieu (1906), Lautier (1908) and Dieulafoy (1909) have given good accounts of this complication. Lautier described three early uncomplicated cases of gonorrhoea in which he cultivated the germs from the blood. According to this author the gonococci reach the circulation through the veins, and most often when the primary lesions involve the posterior urethra or glands connected with it, such as the prostate, seminal vesicles, or testicles. One seldom gets a pure septicæmia. It is associated as a rule with arthritis, endocarditis, meningitis, pneumonia, skin lesions, etc. About 70 per cent of cases recover. Most fatal cases are accompanied with endocarditis. It would appear therefore that the chief danger in this condition is endocarditis.

According to Dieulafoy, profuse sweats are very characteristic of gonococcus septicæmia. There is also an intermittent and remittent or continuous fever. Marked pallor and a sallow tint of skin are characteristic, also weakness, lassitude, sleeplessness and inability to work. Other signs and symptoms may suggest typhoid; thus it is common to find pinkish lenticular spots over the abdomen. Dieulafoy reported a case with typhoid symptoms which was fatal in a week. This case was proved to be a pure gonococcus septicæmia. In two other cases which he described in detail the patients were convalescing from gonococcal septicæmia, when typhoid fever developed. A further case in a young soldier was brought to his notice by Cherrer. This patient had had gonorrhoea for fourteen days, when the temperature rose to 38°, 39° and even 40° C. A pleural effusion developed, and gonococci were found in the turbid fluid. This patient died. Thayer published a similar case. A young man who had gonorrhoea for three months was suddenly taken ill with malaise and fever rising to 104° F. It was thought at first to be typhoid, but the Widal test was negative. A blood culture revealed colonies of gonococci.

Colombini (1898) described a case of gonococcal septicæmia in a man aged 28 suffering from a neglected urethritis. After fourteen days he developed a bubo in the left groin, which was incised, and also a left epididymitis which suppurated. The temperature rose to 39° C. and lasted for two weeks, accompanied with wasting. A metastatic abscess developed in the right parotid gland, which required incision. Gonococci were found in the pus from the urethra, abscess in the groin, scrotum and parotid. They were also cultivated from the blood in two out of three attempts, and the germs were successfully inoculated into the urethra of another youth.

Barbiani (1902) reported a case in which gonococci were cultivated from the blood. The condition resembled acute articular rheumatism.

Courtois-Suffit and Beaufumé (1905) reported a fatal case which followed upon the

repeated passing of catheters in a gonococcal urethritis. A severe infection of the blood supervened, which was characterised by multiple abscesses and ended fatally. In all the abscesses and in the blood, gonococci were found. They were isolated from pus in the right brachial and triceps muscles, from the posterior surface of the sternum, from the left thigh, and from the left testicle and epididymis.

The above case was therefore really a pyæmia.

Schoelor (1908) reported a case in a nurse who had been attending a child suffering with gonorrhœal ophthalmia. She received a slight injury on the right forefinger, in which the skin necrosed and an ulcer developed. Gram-negative diplococci were detected by the microscope in the ulcer. An abscess in the femur followed, and she eventually died of septicæmia. According to the author this is the first recorded case in which the gonococci entered the blood by the skin.

Cholzow (1912) stated that he could only find 8 cases of true gonococcus septicæmia on record during the previous ten years. Cases of "gono-pyæmia," however, as he called them, could be counted by hundreds. A true case of septicæmia which he himself described occurred in a druggist aged 36. There was a history of syphilis contracted in infancy, and also of gonorrhœa contracted at the age of 30. The condition commenced with a chill and high fever, pains in the perineal region, and anuria for a day or two. Swelling and tenderness developed in both wrists and in the right maxillary articulation. Gonococci were isolated from the blood by culture. An abscess was found in the prostate, and evacuated. Vaccine was administered, also saline infusions, and the patient recovered by the fourth week.

Thévenot and Michel (1912) published a fatal case of hæmorrhagic gonococcal septicæmia in a man aged 31 who had had a urethritis for sixteen months. He became suddenly ill, and developed a purpuric rash on the neck and abdomen. He had also hæmorrhages from the nose and mouth, and died shortly afterwards.

Weitz (1912) reported a fatal case in a patient aged 19. It was characterised by severe icterus, hæmorrhages, stupor, fever and albuminuria. Gonococci were cultivated from the blood.

Further fatal cases were published by Moorhead (1912) and Rueck (1913). Nicoll (1915) described three cases of gonococcal septicæmia with arthritis following scarlet fever.

Jenkins (1922) reported the following interesting case:—

A man aged 38 was admitted to the surgical wards at the Paddington Infirmary with acute synovitis of the right knee. A history of gonorrhœa three months previously was supported by the condition of the prostate, which was hard, tender, and nodular; the seminal vesicles were palpable. He ran a temperature of from 102° to 104° F., and appeared more toxic than the local conditions warranted. The knee gradually settled down under treatment.

About two weeks after admission intense pain occurred over the outer side of the right thigh. This pain appeared to be localised to the deep fascia, and an acute metastatic involvement of this structure was considered probable. A few days later venous thrombosis occurred in the superficial femoral vein of the right leg about the middle of the thigh, and the leg became very œdematous. Gentle prostatic massage yielded pus and blood from the posterior urethra, and gonococci were found in the smear; previous examination had been negative. A generalised adenitis throughout the body then occurred. The cervical glands in the anterior triangle of the neck were visibly enlarged and were very tender on palpation, and a free purulent discharge from the urethra commenced.

Ever since admission the patient's temperature had ranged from 102° to 104°, and about three weeks after admission his general condition was much worse. His pulse rate rose at times to 140, and he had frequent rigors, but neither at this time nor in the subsequent course of the disease was there any clinical evidence of endocarditis. A papular eruption appeared at this stage. It was most marked on the extensor surfaces of the

forearms and backs of the hands, and on the legs below the knees ; large hyperæmic spots were also present. These eruptions faded away in the course of a few days. The next complication was the sudden onset of severe pain over the localised area in the region of the internal semilunar cartilage of the left knee-joint. There was no fluid in the joint then, but a few hours later the joint was hot, painful and tender, and was fully distended with fluid. Epididymitis followed next day, and the right testicle became similarly involved a few days later.

Another crop of papules then appeared, associated with large hyperæmic spots half an inch in diameter as before. A blood culture at this time gave a pure culture of gonococci, from which a vaccine was prepared. The rash disappeared in about three days, and with its disappearance there was a slight improvement in his general condition. A week later another series of rigors occurred, associated with a high temperature and prostration. Hyperæmic areas and papules appeared on the arms. Blood culture was again positive for gonococci. One papule on the hand formed a pustule, but no growth of organisms was obtained from the pus. During the course of the disease arthritic pains and slight effusions into practically all the joints of the body took place.

Gradual recovery followed, and the temperature was normal about four months after admission. The patient was discharged to the country about two weeks later, with no disability other than a definite involvement of the prostate gland and seminal vesicles, and considerable œdema of the right leg when up and about. Three months later he reported much improvement in general health, but there was still marked œdema of the right leg, with dilatation of the superficial veins. The prostate and vesicles were in the same condition as on discharge, and he is now undergoing treatment for this.

The case is interesting in view of the excellent recovery in spite of the very widespread involvement and septicæmia (in the absence of endocarditis). The existence of gonococci in the blood stream, and the rash, which appeared to correspond in time with the rigors and septicæmia, seem also worthy of note.

Sacquépée (1922) describes a case in which the septicæmia developed in the first few days of an acute gonorrhœa, following an attack of diphtheria. The condition lasted for four months. The gonococcus was cultivated from the blood at first, and later a streptococcus was grown. There was also a process of pneumonia, for which the pneumococcus was responsible. The pneumonia yielded promptly to anti-pneumococcus serum, and the whole clinical picture subsided after the fourth intravenous injection of anti-gonococcus serum.

Diagnosis.—Suspicion should be aroused with the onset of severe fever occurring in the course of an ordinary gonococcal infection. In uncomplicated gonorrhœa one seldom gets fever. In twelve cases of urethritis Noguès found only one with a slight rise of temperature. In the absence of any acute complications such as epididymitis or prostatitis, and when the condition resembles typhoid fever, with rose spots on the abdomen, one would be justified in making a blood culture.

Faure-Beaulieu (1906) recommends mixing the blood with ascitic broth and allowing to incubate for twenty-four hours. Subcultures should then be made on a good solid medium. One negative blood culture is hardly sufficient for a negative diagnosis. Harris and Johnson failed to grow the germ in two out of five trials on one patient, and Faure-Beaulieu was also unsuccessful in three out of four attempts. It looks almost as if the discharge of gonococci into the circulation took place at odd times, corresponding to the clinical intermittent or remittent attacks of fever.

Gradwohl (1912) suggested that the complement-fixation test would be useful for the diagnosis of gonococcal septicæmia. No doubt it would be useful in some cases where the existence of gonorrhœa was doubtful. Where, however, there was a definite local gonorrhœa, a positive test would be expected in any case, and this would not help one to determine whether or not the infection had gained an entrance to the blood stream. Definite diagnostic evidence can only be obtained from a positive blood culture.

Treatment.—Gonococcal vaccine has given successful results in many cases, and several authors have obtained satisfactory recoveries with anti-gonococcus serum; *vide* chapters on Vaccine Therapy and Serum Therapy. We have so far no definite chemical specific remedy. The gonococcus does not like alkalis, so it might be of advantage to give considerable doses of sodium bicarbonate by the mouth as in rheumatic fever. Salicylates do not seem to exert any definite specific action on gonococcal infections, although a few authors recommend them in arthritis cases. The greatest hope appears to lie in vaccine therapy. In addition, palliative and symptomatic treatment, stimulants when required, and saline infusions, all help to bring about a recovery.

Gonococcal Pyæmia.—According to Cholzow this is a much more common condition than a true septicæmia; at any rate the septicæmia usually develops into pyæmia. It is a more or less rare condition, but many cases have been reported. Babes and Sion (1883) described a case of gonorrhœal pyo-septicæmia with endocarditis. Ullmann (1901) recorded 5 cases of gonococcal pyæmia, in 4 of which the necropsy showed the source of infection to be a prostatic abscess. This would indicate that the condition often arises from latent gonorrhœa.

Wynn (1905) found that cases of systemic gonorrhœa, including pyæmia, showed a leucocytosis like scarlet fever, pneumonia, etc. He obtained gonococci from the blood in 3 cases, in 1 of which they were isolated one hour after death. In all 3 cases the abscesses showed a mixed infection. One showed a combination of gonococci with *B. coli*, and the other 2 showed a triple infection with gonococci, *B. coli*, and staphylococci. One of these cases exhibited miliary abscesses in the lungs and kidneys. Another showed an abscess in the hip, and later all over the body. Vegetations were also found on the heart valves, and gonococci were present in these vegetations. The third case, which was also fatal, showed pelvic cellulitis, but the peritoneum was not involved.

Hall (1905) described a case of general gonococcal infection in which the joints, pleura, and muscle sheaths were all affected. No culture, however, was made.

Jacob (1907) recorded a fatal case in a patient thirty-five years old. There were numerous abscesses, endocarditis and pleurisy. The joints were also affected and the skin was covered with miliaria. The pus from the pleural cavity and from the abscesses showed large numbers of typical gonococci. This is one of the few cases in which a detailed blood count has been given, as follows:—

3,376,000 red corpuscles. Hæmoglobin 55 per cent.	
12,600 white corpuscles.	
Polymorphonuclear cells	248, or 62 per cent.
Lymphocytes	138, or 34·5 „
Mast cells	10, or 2·5 „
Eosinophiles	4, or 1 „

A differential cell count of the pleural fluid showed —

Eosinophiles	147, or 28·3 per cent.
Mast cells	123, or 23·9 „
Endothelial cells	112, or 21·5 „
Lymphocytes	112, or 21·5 „
Polymorphonuclears	25, or 4·8 „

The post-mortem revealed ulcerative endocarditis of the aortic and mitral cusps.

Weiner (1912) described 2 cases of gonococcal septic pyæmia following upon a gonococcal infection of the rectum (proctitis). The first case was in a woman who separated from her husband three days after her marriage. Since then for one and a half years she suffered from bad health, with swelling of the feet and ankles and shivering, feverish attacks (temp. 39° C.). Heart murmurs were present with a rapid pulse. Albumin, pus, and granular and hyaline casts were present in the urine. Red cells numbered 3,760,000

per c.mm., and the leucocytes 6700 per c.mm. She eventually developed anuria, œdema and ascites, and died. The post-mortem showed ulcerative proctitis due to chronic gonorrhœa with a stricture five centimetres above the anus. There were also thrombi in the vena cava inferior and in the renal veins. Infarcts were found in the lower lobes of the lungs and the upper lobe of the right lung, and also emboli in the pulmonary arteries. There was diffuse nephritis, uræmia, dropsy, amyloid degeneration of the kidney, spleen and intestine. This illness had arisen in the course of one and a half years from a gonococcal proctitis.

The second case was in an eighteen-year-old girl with a temperature 39.8°C ., irregular pulse and quick breathing. She also showed an enlarged and painful spleen. Gonococci were found in the pus from the Bartholin glands. She died with hyperpyrexia and convulsions. The post-mortem showed degenerative parenchymatous myocarditis and pneumonia with red hepatisation. There was a septic swelling in the spleen with infarcts due to septic emboli, also degeneration of the liver with many infarcts. In the lower part of the rectum there was a chronic destructive catarrh with ulcers and fistulas which communicated with the Bartholin glands.

Tudehope (1913) reported a case which recovered. The diagnosis was made by a process of exclusion. Gonococcal vaccine was administered, commencing with 50 millions and rising to 400 millions.

Diagnosis and Treatment are the same as for gonococcal septicæmia.

Metastatic Abscesses.—Under the heading of gonococcal pyæmia we may include *metastatic gonorrhœal abscesses of the subcutaneous connective tissues*. The presence of gonococci in such abscesses has been definitely proved by culture, by Horwitz (1893), Bujwid (1895), Hansen (1900), Young (1900), Wynn (1905), Hocheisen (1906) and Jacob (1907).

Campbell (1908) published the case of a youth of eighteen who sustained a compound fracture whilst he was suffering from an attack of gonorrhœa. Considerable suppuration set in at the site of the fracture, and the pus yielded cultures which contained gonococci. He believed that in this case the fracture was infected by gonococci which had reached it through the blood stream.

The following authors described cases, but the proof was only microscopic.

Ware (1901) obtained bloody fluid from an indurated area in the post-scapular region, in a patient with a history of gonorrhœa. The smears of the fluid showed Gram-negative diplococci, but cultures on ordinary media gave no growth.

Cassel (1903) described a case in an infant which developed purulent ophthalmia shortly after birth, followed by gonococcal arthritis and later by an abscess in the back. Microscopic examination of the pus showed typical gonococci.

Harris and Haskell (1904) reported a case of gonococcal abscess in a woman who had boggy swellings at the junction of the lumbar and sacral regions of four months' standing, and a marked fluctuating swelling of the calf of the right leg. The material aspirated from the swellings contained the gonococcus.

Kerassotis (1904) reported on a metastatic mastoid gonorrhœal abscess in a man aged twenty-five who was suffering from gonorrhœal urethritis. The pus obtained after incision of the mastoid showed gonococci microscopically.

Further, we may include *metastatic abscesses in the muscles*; in these gonococci have been demonstrated culturally by Strong (1904), as well as by Harris and Haskell (1904). Heller (1902) and Becker (1905) also described cases of suppurative gonococcal myositis without cultural proof.

Diagnosis.—It is necessary to demonstrate the gonococci in the pus by microscopic examination of smears stained by Gram's method. More certain proof is obtained by actually cultivating the germs from the pus on a suitable medium.

Treatment consists essentially in evacuation and drainage of the abscesses.

Gonococcal Endocarditis.—There has been published a large number of undoubtedly

proved cases of fatal gonorrhœal endocarditis. In these cases cultural proof of the presence of gonococci in the inflammatory vegetations of the endocardium was obtained at the post-mortem.

Communications on such cases have been given by Thayer and Blumer (1896), Rendu and Hallé (1897), Honl (1899), Thayer and Lazear (1899), Michaelis (1901), Wassermann, M. (1901), Harris, Norman McLeod and Dabney (1901), v. Frendl (1903), Prochaska (1901 and 1905), Hunter (1905), Rulbs and Jacob (1907).

In 10 of these cases the aortic valves were affected, and only in 2 cases were the tricuspid valves involved.

Ghon and Schlagenhauser (1898) produced a typical urethral gonorrhœa in a healthy subject with a pure culture of gonococci obtained from an inflamed gonorrhœal aortic valve.

Lenhartz (1897) obtained a culture of gonococci by inoculating the medium with the thrombus pulp of an inflamed pulmonary valve, thereby proving the gonococcal nature of the disease. Gonococci have been demonstrated in the circulating blood of patients suffering from gonorrhœal endocarditis, by Reye (1903), Krause (1904), Duval and Lewis (1905), Widal (1905), Thayer (1905) and Horder (1905). According to a compilation by Faure-Beaulieu (1906) 12 severe cases of endocarditis (70 per cent mortality) occurred out of 34 cases of gonococcal septicæmia (with proof of gonococci in the blood).

Ullmann (1901) had a case of fatal gonococcal endocarditis which developed severe jaundice when the end was near.

Hamilton (1905) described a case of gonorrhœal endocarditis, but proof was lacking, as no culture was made.

Horder (1905) cultivated the gonococcus from the blood of his case on two occasions, three and a half months after the onset of his original attack of gonorrhœa. The patient died.

Rothrock (1911) reported on a case of gonorrhœal endocarditis which developed during convalescence after a series of gynecologic operations. The patient had a recent gonorrhœa, and it was found necessary to use a catheter on a few occasions immediately following the operation. Rothrock considered it was possible that the passage of the catheter over the inflamed mucous membrane of the urethra opened a way for the passage of the gonococci into the blood stream, or it may have been that it dislodged a small infected thrombus.

Gill (1913) reported on an acute fatal endocarditis following gonorrhœa, but gonococci were not found bacteriologically.

Satterthwaite (1913) analysed 100 cases of endocarditis in children in New York city hospital and found only 1 case due to gonorrhœa.

Dunn (1913) collected 304 instances of endocarditis in children, and in no case was the disease due to the gonococcus. This is sufficient to show that gonococcal endocarditis is a very rare disease.

According to Besson (1914) the gonococcus has been found in endocarditis lesions by Berg, Lartigan and others.

Luithlen (1915) described a case which he successfully treated with intravenous injections of gonococcal vaccine.

According to Luys (1917) the onset of gonococcal endocarditis is sometimes sudden and characterised by fever or by syncope, but in most cases its beginnings are insidious. The acute stage is comparatively short, but it often leaves incurable permanent lesions. It is by far the commonest cardiac complication of gonorrhœa, and is usually preceded by articular lesions.

Histologically the lesions are those of a simple or of an ulcerative endocarditis with destruction and perforation of the valves. The right heart is often involved.

In the 31 cases collected by Thayer and Lazear, the lesions were distributed as follows :—

Left heart	Aortic	12	} 67.7 per cent.
	Mitral	6	
	Both	3	
Right heart	Pulmonary	7	} 25.8 ..
	Tricuspid	1	
Both sides of heart		2	6.4 ..

Gonorrhœal endocarditis chiefly affects adults, and in particular, men. Its onset may occur any time, *i.e.* soon after the commencement of the gonorrhœa, or years afterwards.

Benson (1918) reported a fatal case of gonococcal endocarditis. The patient, aged 19, was admitted to hospital with an acute attack of gonorrhœa of three days' duration. The blood count showed 13,800 leucocytes per c.mm., with 74 per cent of polymorphs. The acute symptoms subsided in a few days and the patient was out of bed, when he began to complain of pain and tenderness in the right ankle. There was a slight rise of temperature, and he was put to bed again. The leucocyte count was 14,000 per c.mm. The symptoms grew rapidly worse, then subsided, only to reappear with equal severity a few days later in the right elbow. The migratory character of the disease was shown in the subsequent involvement of the right shoulder, right wrist and left knee. Ten days after the patient had taken to his bed with arthritis, he had a sudden rise of temperature with weakness, dyspnœa and some præcordial discomfort. Heart murmurs were detected over the apex. The leucocyte count rose to 17,000 per c.mm., with 78 per cent of polymorphs. Blood cultures were negative. After some days the patient grew progressively worse. The temperature rose to 103.8° F.; he became orthopnœic, profoundly toxic, and died. A post-mortem was refused, but after death a few c.c. of the heart blood were aspirated and inoculated on to plates of glucose ascitic agar and starch agar. Pure cultures of the gonococcus were obtained.

Dwyer (1920) gives a very careful account of a fatal case in a girl aged 23 months. She entered hospital with painful swelling of the left ankle and wrist and a temperature of 105° F. Three weeks before admission the left foot was swollen, and a vaginal discharge was noticed. On admission, examination revealed a superficial lumbo-sacral abscess two inches in diameter. There was a vaginal discharge, smears of which showed many Gram-negative intracellular diplococci. The abscess was opened aseptically, and the pus showed Gram-negative intracellular diplococci. Inoculations on Loeffler's blood serum yielded no growth.

The lungs were normal, but the abdomen was distended and tender. A systolic murmur was heard over the entire cardiac area. The spleen was enlarged to two inches below the costal border. Ten c.c. of blood were drawn aseptically from the median basilic vein and cultivated in ascitic glucose broth and on ascitic glucose agar. At the end of 60 hours' incubation a Gram-negative diplococcus was grown.

A blood count gave 19,000 leucocytes per c.mm. with 89 per cent neutrophils, 2 per cent large lymphocytes, and 9 per cent small lymphocytes. The hæmoglobin was 80 per cent. The temperature was very irregular, varying from 101° to 105° F. The pulse varied from 140 to 160 beats per minute. The cardiac murmur became harsh, and after seven days in hospital, on the 28th day of her illness the patient died. The post-mortem showed no evidence of peritonitis; the liver was not enlarged, but the spleen was large and soft. The pericardium contained a moderate amount of serous fluid. The heart lesions were confined to the mitral valve, and on the free border of each cusp were greenish-yellow cauliflower vegetations. The posterior cusp was perforated by a circular opening 6 mm. in diameter. Smears from the valves showed Gram-negative diplococci. Sections of the valves showed areas of ulceration with an accumulation of amorphous material attached to the surface. Surrounding the necrotic area there was a zone of inflammatory reaction and cellular infiltration. Many of the infiltrating cells were of the polynuclear variety.

In other areas the endothelium was intact, but beneath it the tissue was found to be degenerating, indicating that it would soon have broken down to produce further areas of ulceration. The muscular tissue was also somewhat involved, as shown by the tissue infiltration. A few coffee-bean-shaped diplococci were found beneath the ulcerated areas.

Lion and Lévy-Bruhl (1922) give brief notes of five fatal cases of gonorrhœal endocarditis recorded by French and American authors, four patients being young men and one a little girl aged nearly two years. In addition to these, 58 cases have been collected by Sagot, who found endocarditis only on the left side of the heart in 48 cases. The aortic orifice only was attacked in 27 instances; both aortic and mitral lesions were found in 8 cases, while in 13 others the mitral valve only was affected. In 6 cases lesions were on the right side of the heart, while in 4 others both sides of the heart were affected. Only 26 per cent of the patients were females. They now record the case of a woman, aged 29, who had a healthy child aged 8, and no subsequent pregnancy. She was admitted to hospital on 29th October 1920, having been confined to bed since the onset of generalised rheumatism two months previously. After treatment by sodium salicylate, swelling and pain disappeared from all joints except the left shoulder. Fever, however, persisted, the temperature rising every evening, with shivering followed by profuse sweats. She was emaciated, weak and anæmic, with a generalised chronic dermatitis, especially over the knees, and scanty mucous sputum with a few scattered bronchitic râles heard at the back. The patient complained of occasional palpitation. The heart was dilated, the apex-beat being in the fifth interspace outside the nipple line. Pulse 96, regular. In the "aortic" region a soft blowing diastolic bruit with maximum intensity at the base of the xiphoid was heard; here there was also a faint systolic bruit, and a hæmic murmur over the jugulars. Nothing abnormal was found in the abdomen except that the spleen was just palpable. She had no appetite, and took no food but a little milk. The stools and urine were normal. The symptoms persisted; vomiting commenced three days after admission, and she died on the fifth day. At the autopsy no signs of disease were found in either abdominal or genital organs. The heart showed a large vegetation on the posterior aortic valve, but no other valvular disease. Blood cultures on ordinary bouillon made on admission and two days afterwards were negative, but serum obtained on the day after admission produced marked agglutination in a typical laboratory culture of gonococci. The technique (Maurice Nicolle) is minutely described. Under the microscope the pericardial fluid, heart blood, and fragments of the vegetation removed aseptically at the autopsy all showed very numerous Gram-negative diplococci morphologically identical with gonococci; these were also found on section in scattered groups or in large masses in the partially organised granulation tissue of the vegetation from the aortic valve. No other micro-organism was found. Only one fragment of this vegetation yielded a growth on an ordinary medium; this was transferred to ascitic agar and resulted in an abundant growth of typical diplococci. The authors consider that the occurrence of gonorrhœal endocarditis, though rare, can no longer be doubted, and state that the lemon-yellow pericarditic effusion of moderate amount (in which they found numerous gonococci) is pathognomonic, and that the purulent pericarditis described by some authors is exceptional. They discuss the clinical symptoms and bacteriological findings, and emphasise the statements of several observers—that blood cultures frequently fail; for this reason the agglutination test is preferred as being more reliable, enabling an earlier diagnosis to be made, when vaccine or serum therapy may arrest the disease before irreparable damage has resulted.

Diagnosis. Cardiac signs and symptoms developing in the course of an attack of gonorrhœa should make one suspicious. Definite proof during life, however, can only be obtained by cultivating the gonococci from the blood. Other metastatic complications, such as arthritis, are often present. *Vide* also Gonococcal Septicæmia.

Gonococcal Myocarditis.—According to Luys (1917) this condition never occurs alone, but is always associated with endocarditis or pericarditis. The histological find-

ings have established beyond doubt that the gonococcus migrates into the endocardium and into the myocardium. One finds in the latter, areas of leucocytic infiltration, embolic abscesses, and necrotic patches, which contain gonococci.

Gonococcal Pericarditis.—Cases of gonorrhoeal pericarditis have been reported by Bordoni-Uffreduzzi (1894), Prochaska (1901), Ullmann (1901), Silvestrini (1904), Huber (1904), Becker (1905) and Crosby (1905). In all of these, however, the gonococcus was not demonstrated in the pericardial exudate by culture, so absolute proof is lacking.

Bubis (1908) described a case of acute pericarditis following the removal of a gonorrhoeal pyosalpinx. The author has been unable to get access to his paper.

Luys (1917) states that this complication is far less common than endocarditis, and takes occasionally a very mild course. In most cases there are definite symptoms such as palpitation, præcordial pains and dyspnoea. The physical signs are those of a dry pericarditis or of a pericarditis with effusion. The affection is usually benign, and terminates as a rule by resolution.

Treatment.—The local focus of gonorrhoea in the uro-genital tract must be dealt with. Also general treatment with gonococcal vaccines, combined with the usual symptomatic treatment for the heart condition, such as counter-irritation over the præcordium, stimulants, etc.

Gonococcal Pleurisy.—Mazza, quoted by Bordoni-Uffreduzzi (1894), succeeded in cultivating gonococci from a case of gonorrhoeal pleurisy in a young girl of eleven who had been raped.

Bertrand (1895) published the case of a woman who, on the seventh day of her gonorrhoeal vaginitis, developed a pleurisy with effusion. Examination of the fluid, according to this author, revealed the presence of the gonococcus.

Further communications on this complication are given by Guiard (1898), Hansen (1900), Prochaska (1901), Paldrock (1900), Hall (1905) and Crosby (1905).

The fatal case of gonococcal pyæmia described by Jacob (1907) showed a purulent effusion in the pleural cavity. On microscopic examination large numbers of typical gonococci were found in the pus cells. The differential cell count made on the pleural fluid of this case is given under the paragraph on gonococcal pyæmia.

Géraud (1912) published an interesting case of gonorrhoeal empyema in a young man of 19 who had a profuse urethral discharge. The bacteriological examination of the pus withdrawn by aspiration from the chest gave a pure culture of the gonococcus.

Thoracocentesis was performed and led to a complete cure. This is the first case of purulent gonococcal pleurisy which had been cured by surgical intervention.

According to Luys (1917) all the cases of gonococcal pleurisy described showed a moderate amount of exudate. The condition is usually unilateral, but shifts in a remarkable manner. The effusion comes on in a few hours, and tends to disappear with equal rapidity.

Woodberg (1918) cites a case of a girl aged 8 years, whom he operated upon for general peritonitis which he thought was due to a perforated appendix. On the sixth day after the operation there were signs of dullness behind the base of the right lung. A few c.c. of pus were obtained by thoracotomy. The child died 12 hours later. There was no post-mortem. On the second day after the first operation the child was found to have a profuse yellowish vaginal discharge. Smears showed only gonococci. Blood cultures were negative. Smears of the pus from the chest showed gonococci, but attempts to cultivate them were unsuccessful, as the culture tubes remained sterile. The author considers that this was a case of gonococcal empyema.

Diagnosis.—Evidence of pleurisy, with cultural proof.

Treatment, as described under gonococcal septicæmia, with the usual treatment for pleurisy in addition.

Gonococcal Pneumonia.—Bressel (1903) recorded a case of pulmonary gonorrhoeal inflammation. The gonococci were only demonstrated microscopically in the lungs, but on the other hand they were cultivated from the circulating blood.

Finger (1905) mentions a case of fatal broncho-pneumonia of gonorrhœal origin.

Wynn (1905), as already mentioned, succeeded in cultivating gonococci from miliary lung abscesses which occurred in a case of gonococcal pyæmia.

Ross (1919) described a case of pneumonia in which the organism obtained from the blood, the sputum, and from direct puncture of the lung was a Gram-negative diplococcus which grew in pure culture. This patient had an acute exacerbation of a chronic gonorrhœa at the time. The lobar pneumonia followed an atypical course. The sputum was scanty, very tenacious, milky-white, with no trace of blood at any time. The lung process terminated in pulmonary abscesses.

Gonorrhœal Phlebitis and Arterial Thrombosis.—This condition has been observed by Batut (1901), Heller (1904) and Voss (1905). According to Heller, there were in the literature, up to the time of the publication of his work, accounts of 25 cases of gonococcal thrombo-phlebitis. Of these cases, 20 were men and only 5 were women.

Moore (1903) described a fatal case of gonorrhœal arterial thrombosis of the aorta and of both common iliac arteries, as well as of the left renal artery.

The gonococcus, however, was only demonstrated in part of the above cases, and this only by the microscope and not by culture.

Zesas (1909) reported a case of gonorrhœal phlebitis in a man aged 30, with chronic gonorrhœa which had resisted all forms of treatment for a year. Phlebitis suddenly developed after a long walk.

Schlagenhauser (1910-12) wrote a special chapter dealing with the literature on gonococcal phlebitis in the handbook of venereal diseases by Finger, Jadassohn, Ehrmann and Gross.

Rotky (1912), in a fatal case of general gonococcal infection, found thrombosed veins in the sections of pus-foci over the metatarso-phalangeal joint of the left great toe. The walls of these veins showed acute inflammatory changes.

Zigler (1914) recorded a case of phlebitis of the penis, complicating acute gonorrhœa and simulating œdema induratum.

In 1915 he contributed a further paper on a case of gonorrhœa with unusual complications, viz. phlebitis and epididymitis.

GONOCOCCAL AFFECTIONS OF THE BONES

[(1) **Gonorrhœal Periostitis and Osteo-periostitis.**—The occurrence of purulent gonorrhœal periostitis was definitely proved by culture in the case described by Finger, Ghon and Schlagenhauser (1894).

According to Hirtz (1900), Fournier, in his remarkable study appearing in 1869, first established definitely the clinical existence of periosteal manifestations of gonorrhœa. He distinguished between *periostitis* and *periostosis*, the former being simple inflammatory deposits in the periosteum, and the latter being tumours resulting from infiltrations between the bone and the periosteum. He insisted on the much greater frequency of periostitis, as is frequently associated with the deforming variety of gonorrhœal arthritis.

Ozenne (1895) reported on a case of gonococcal periostitis on the inner surface of the tibia, accompanied with synovitis in the tendon sheaths of the extensor muscles of the foot.

Claisse (1897) also described a case of osteo-periostitis.

Durand and Nicolas (1907) were inclined to think that the thickening of the bones in deforming gonococcal arthritis was due to the inflammatory infiltrations of the tissues outside the periosteum, and they consider that this condition cannot be compared to that of an osteo-myelitis, since there is no suppuration or sequestration.

The following case, however, described by Watts, as well as others in the literature, shows that the gonococcus can produce marked changes in the bone and periosteum.

Watts (1911) stated that gonococcal osteo-periostitis of the epiphyses, and especially of the smaller bones of the hands and feet, was not very uncommon. On the other hand, this condition was very rare in the diaphyses of the long bones. Some even disputed the existence of the latter condition. The following case described by Watts, however, proved that it can occur. The patient gave a history of swelling in the left thigh of two weeks' duration. It was painful, hot and hard. There was no history of injury. He had night sweats which dated back to a gonorrhœal infection of four weeks' duration. A bubo developed in the left groin but disappeared again without discharging. The temperature rose to 103.6° F., and a blood count showed 12,000 leucocytes per c.mm. The acute urethritis had dried up a week after the disappearance of the swelling, but he still showed a purulent balanitis, and gonococci were found in the pus. The patient was operated upon, and the swelling was found to be due to a small collection of fluid beneath the periosteum of the femur. This fluid was turbid, but not actually purulent, and a pure culture of gonococci was grown from it. The periosteum was very thick, cedematous, and lined with velvety granulation tissue. It was separated from the bone by the fluid. The exposed bone was slightly thickened and roughened by new bony deposits. The marrow cavity was not opened. Sections of the periosteum revealed no definite gonococci, and the appearance resembled that shown by any other granulation tissue. Skiagrams showed definite deposits of bone over the femur, and later a thick envelope of new bone developed around the shaft, extending from a short distance below the trochanter almost to the condyles. Seven months later the skiagrams revealed a greatly thickened femur. After this he lost sight of the patient.

Picker (1911) described a case of ankylosing spondylitis and various bone changes occurring in the course of a chronic gonorrhœa. The patient, aged 31 years, had his first gonorrhœa ten years before, with a second attack four years later. Still later the condition was complicated with epididymitis and adenitis. A week later he developed a pain in his shoulder, as well as in his heels and metatarsal joints, which lasted for two years. Three years later he got an injury to his left knee, and then there developed for the first time pain and stiffness in his spine. In May 1911, in the course of a new gonorrhœal infection, it was found that a painful swelling had developed at the base of the neck with limited movement of the left shoulder. The back was also stiff and painful. Skiagrams showed that the cervical vertebræ were normal, but the cartilaginous discs of the dorsal vertebræ were thinned. The rib joints from the sixth rib downwards were calcified, as were also the ligaments of the lumbar vertebræ which resulted in limited flexibility of the spine. The left sacro-iliac ligament was also quite calcified.

Rotky (1912) had a fatal case of gonococcal polyarthritis in which there was pain and stiffness in the cervical portion of the spine. He states that gonococcal disease of the vertebral joints is known to occur, but according to Nobl (1910-12) this is one of the rarest complications.

Hahn (1911), in a paper on gonorrhœal rheumatism, states that the gonococcus seems to have a special predilection for the periosteum, and that the latter when attacked is stimulated to produce exuberant granulations.

Villapadierna (1917) described a case of gonococcal periostitis in a robust young woman. In the second week of an acute gonorrhœal attack she developed pain at the front of the lower half of the tibia. The skin was apparently normal, but the region was tender along with the local pain. With rest the condition became gradually less painful until only a small patch of tenderness remained at the end of a week. The knee then became affected in the same way, the inflammation being restricted solely to the internal condyle of the femur, with the rest of the joint normal. There were no signs of syphilis, but gonococci were numerous in the urethra and vulva. With intravenous injections of sodium salicylate improvement followed, and soon no trace of the periostitis was left. The above author was unable to find any other case on record in which the process was restricted exclusively to the periosteum. Cases of pain in the heel bone, for

which the gonococcus was responsible, have, however, been published, and in a similar case (unpublished) the clavicle was affected in the same manner.

Luyts (1917) states that the parts most commonly involved with gonococcal periostitis are the tibia, the epitrochlea, the lower end of the ulna, the upper end of the fibula, etc., or—in a few words—the bony projections of the skeleton. As a rule the patient complains of a sharp pain in the bone, which is definitely limited to a small area the size of a shilling or less. It is not uncommon to find a slight doughy swelling, and sometimes an inflammatory reddening of the integuments. After a few days' duration these phenomena subside and disappear. Sometimes, however, these cases of periostitis do not terminate by resolution but form true tumours which become periostoses. They are flattened, fixed, hard, small resistant swellings, firmly adherent to the bone. At first they give rise to a certain amount of pain, but they soon become less and less sensitive.

(2) **Gonorrhœal Exostosis of the Os Calcis.**—Baer (1906) was the first to prove definitely that this condition was due to the gonococcus.

Jacquet (1902) and Painer described exostosis on the posterior calcaneal surface, but were unable to determine the etiology of the condition.

Ely (1905) referred to a condition which he called "gonorrhœal foot," and states that it "is characterised by extreme sensitiveness, usually in the soles, and the patient walks as if treading on eggs. A history of recent gonorrhœa is usually obtained." It is quite possible that Ely was referring to cases of gonorrhœal exostosis, but he reported no skiagraphic or pathological findings.

Nobl (1906) was quoted by Baer as having previously noted exostosis on the posterior surface of the os calcis, and he had suggested that they might perhaps be of gonorrhœal origin.

Baer (1906), however, was the first definitely to describe and prove the gonorrhœal origin of the condition, which he termed "gonorrhœal exostosis of the os calcis." He believed that the initial process was located in the flexor brevis digitorum muscle, and that it extended down to the bone. The chronic inflammation produced exostotic growths at the attachment of the muscle to the tubercle of the os calcis, and secondly, other bony growths sometimes developed on the sides and posterior surface of the calcaneum, or in the adjacent tendons. He operated upon 5 cases and removed the diseased tissues. Bacteriological examination in 4 of these cases revealed the gonococcus by culture in 1 and by microscopic examination of sections in the other 2, so that 3 out of the 4 were positive. Baer states that the condition is characterised by pain over the plantar surface of the heel.

Jaejer (1908) reported on 11 cases, and considered that the process was an ossifying periostitis. Gonorrhœal arthritis and exostosis between and among the vertebræ may be coexistent. He reported positive findings of gonococci in 1 of his cases.

Davidson (1908) recorded a further case, but cultures taken proved to be sterile.

Winthrop (1909) reported on 2 cases of gonorrhœal exostosis of the os calcis. He states that this affection is probably not uncommon, but the chief symptom, that of pain under the heel, is usually ascribed to some other condition—flat-foot, tuberculosis, osteo-myelitis, sarcoma of the bone, neuritis, bursitis, chronic rheumatism, rheumatoid arthritis, Schaffer's foot and the various other conditions associated with painful heel—and the close relation of any existing or previous gonorrhœa is overlooked. Very often there is an existent gleet or a history of acute urethritis some months previously, generally three to nine months. Skiagrams show a pointed or slightly bulbous bony growth, from the size of a pea to a marble, springing from the tubercle of the os calcis. Winthrop's 2 cases both showed gonococci in the pus cells in the urine, but the heel condition was not examined bacteriologically.

Merrit (1917) described 3 cases, and believed that this painful condition was often placed under the erroneous diagnosis of arthritis. He maintained that the "ossifying periostitis leads to the formation of bony excrescences, exostoses or osteophytes. First

there is a proliferation of the osteogenic layer of the periosteum, then partial ossification, and finally complete bone formation with firm attachments to the underlying bony structures. The osteogenesis is essentially the same, but the periosteal bone-depositing cells are working in a tissue which is the seat of productive fibrosis, so that the calcium salts are not laid down in an orderly manner along the surface of the bone. These changes may be circumscribed or diffuse, and cause irregular elevations or general thickening of the bone. The exudate may be merely fibrous tissue or a soft albuminous material, usually leading to periosteal thickening, but occasionally invading the bone marrow."

He further states that the usual modes of invasion by the gonococcus of the remote bony structures were either lymphogenous or hæmatogenous. Other bony structures were not exempt from invasion, and especially was this true of the vertebral column. This author gave a very good skiagram of one of his cases of exostosis of the os calcis; this case had also gonorrhœal arthritis in both ankles.

Treatment.—This consists in the cure of the gonorrhœal infection of the urethra and its accompanying organs, as well as the operative removal of the exudate and inflammatory tissue at the site of the os calcis.

(3) **Gonorrhœal Osteo-mylitis.**—Ullmann (1900) described a case of purulent gonococcal osteo-mylitis. This condition occurred in the third week of a second attack of gonorrhœa. The lower end of the left humerus was affected, and pus from the marrow cavity showed gonococci. Ullmann considered that more cases of osteo-mylitis were due to the gonococcus than was generally imagined.

Heymann (1900) described a case in which the lower end of the tibia was affected. At the operation pus was found in the marrow cavity and gonococci were demonstrated in the cells. The patient had had gonorrhœa of one year's standing with prostatic trouble.

Cupler (1907) reported on a case in which the left shoulder-joint was affected. Gonococci were found in the joint, and there was also a cavity in the head of the humerus.

Watts (1911) was unable to find any record in the literature of any cases beyond the three described above, and he considered that Cupler's case was merely a secondary direct extension of the disease from the joint, and not a true primary osteo-mylitis. It is obvious, therefore, that gonococcal osteo-mylitis is an extremely rare condition.

Treatment.—Operative, as well as treatment of the gonorrhœa in the genito-urinary passages.

Gonococcal Joint Affections (Arthritis).—This is by far the most common of all the gonococcal metastatic affections. Neisser and Scholtz (1903) estimated that 0·7 per cent of all cases of gonorrhœa developed this metastasis.

Luys (1917) states that about 2 per cent of all cases of gonorrhœa develop a metastatic arthritis. Gonococcal arthritis resembles more or less the condition produced by other pyogenic organisms. Thus a serous or purulent effusion is produced. The gonococcus very probably multiplies in the synovial membrane itself, and may lead to purulent destruction of this membrane, and even of the ends of the bones.

Communications on gonorrhœal joint inflammations complicating the ordinary uro-genital affections in men or women, and where the germs were demonstrated culturally in the exudate of the joints, have been given by the following authors:—

Bordoni-Uffreduzzi (1894), E. Neisser (1894), Finger, Ghon and Schlagenhauser (1894), Jundell (1900), Meyer (1903), Unger (1901), Young (1900), Nattan-Larrier (1904), Mosny and Beaufumé (1904), Nobl (1903), Wynn (1905), Schultz (1906), and numerous other workers.

In a large series of cases Nasse and Rindfleisch, and also Baur (1901), demonstrated that by a suitable technique the gonococcus could be cultivated from the affected joints in about two-thirds of the cases. Thus Nasse and Rindfleisch (1897) obtained pure cultures from the joints in 19 out of 30 cases of gonorrhœal arthritis, and Baur in 19 out of 27 cases. To obtain success they found it was necessary to make cultures from the fluid in recent

cases, as the gonococci often died out quickly in the joint exudate. Baur was never able to cultivate the organism from the fluid later than the sixth day after the commencement of the arthritis. The germs, however, proliferate and may remain alive for a long time in the synovial membrane. With regard to mixed infections they would appear to be very rare. Baur found a mixed infection with staphylococci in only one case, still more rarely does one find staphylococci and streptococci alone, without gonococci. Nasse and Rindfleisch also considered that mixed or secondary infections played very little part in this disease.

The writer has cultivated the gonococcus from the joint fluid in some ten cases of gonorrhœal arthritis. The cultures in all cases were pure. It is important to use a very good variety of culture medium, and the inoculated tubes should be kept in the incubator for at least ten days. If no growth appears on the third to the sixth day of incubation, one is apt to discard the tube as a failure, but on two occasions in the writer's experience the gonococcus colonies did not develop until the seventh day, and on a third occasion not until the tenth day. This is sufficient to indicate that it is necessary not to discard a tube as negative until a considerable time has elapsed.

From these researches one is entitled to conclude that all or almost all pronounced cases of arthritis in the course of a gonorrhœal attack are produced exclusively by the gonococcus, and that in early cases at least other pyogenic organisms (secondary infections) are seldom found. Further, it would appear that even slight rheumatic pains and transient arthritic swellings are also produced by the germ settling down in the joints. At any rate, there is no proof that the circulating toxins of the gonococcus are alone responsible for these signs and symptoms.

As a rule the gonorrhœal metastasis in the case of the male arises first in the course of a gonorrhœal infection of the posterior section of the urethra. It may arise sometimes, however, from a case of true anterior urethritis. Nobl has observed gonorrhœal joint affections occurring in the course of a vulvo-vaginitis infection. Gonorrhœal arthritis following after ophthalmia neonatorum with demonstration of gonococci in the joints by culture has been described by Hoeck (1893), also by Altland (1902), Paulsen (1905) and Brehmer (1905), with microscopic proof.

Weiss and Klingelhoefter (1897) described a case of gonorrhœal rheumatism in a male nurse, age 35, occurring five weeks after an attack of gonococcal ophthalmia, contracted whilst attending a patient. There was, however, no cultural or microscopic proof in this case.

Emmett (1905) reported on the occurrence of an epidemic of gonorrhœal arthritis in young children among whom were 19 males. In only one of them was there evidence of a gonococcal infection elsewhere—viz., a case of ophthalmia. Repeated cultures, made with the object of determining the point of infection, from the urethra, nose, eyes and mouth, all proved negative.

According to Luys (1917) a gonococcal infection of the seminal vesicle appears to be especially prone to act as a starting-point for gonorrhœal rheumatism. Its thin walls and its rich vascular supply render its inflammation very dangerous and liable to reach the blood stream. The vesicle is thus the organ from which the gonococci are set free and bring about a pyæmia. This opinion has also been supported by Fuller (1909), who resorts to vesiculotomy as soon as gonorrhœal rheumatism supervenes. Whilst in man the seminal vesicles are the usual starting-point of gonorrhœal rheumatism, systemic gonococcal infections giving rise to articular lesions are usually observed in women after they have developed a gonorrhœal salpingitis.

Gonorrhœal arthritis may be regarded as one of the local signs of a gonococcal septicæmia or pyæmia. As a rule the condition is accompanied with a septic swinging temperature. Very frequently only one joint is affected, but sometimes it goes on to a polyarthritis. Almost any joint can be infected, but the knees are the most susceptible to attack. The literature on the subject of gonorrhœal arthritis is extremely abundant.

It has been discussed in a very exhaustive manner by Nobl in the chapter on "Metastatic Gonorrhœal Affections," in the *Handbook of Venereal Diseases* by Finger, Jadassohn, Ehrmann, and Gross. In the classification given in this work on the frequency with which the individual joints are affected, it is found that the knee joint is undoubtedly the most susceptible. Next come the ankle and wrist joints, as well as those of the fingers and the great toe. The next most liable to attack are the elbow, shoulder, hip, and, lastly, the temporo-maxillary joint.

Chaffard and Feisinger (1909) stated that the gonococcus maintained itself very obstinately in the fibrous tissues about a joint, and often left a local fibrosis even after the germ had died out. Rarely an abscess formed yielding pure cultures of the germ.

Stockman (1911) maintained that the incidence of gonorrhœal rheumatism could often be traced to an exposure to cold and wet, or to an injury or strain. In other words, any condition which weakened the vitality temporarily gave the germs an opportunity of settling down and proliferating. He found that the joint exudate contained polymorphonuclear leucocytes, and that it was often thick and turbid, but seldom actually purulent.

Leede (1911) reported a case resembling one of Jadassohn's in which the urethra seemed to be intact, and where the general infection occurred through an erosion in the skin. The patient developed a fatal purulent hæmorrhagic arthritis in the ankle joint. Leede ascribed the severe symptoms to a peculiar idiosyncrasy to the toxins generated by the gonococci, causing stupor, cachexia, extreme atrophy of the muscles, desquamation, and fatty degeneration of the heart. He failed to cultivate the gonococcus from the blood. He described a similar case where the elbow joint was attacked. This time he drained the joint and released the toxins, and the patient recovered.

Hahn (1911) maintained that the prognosis was often bad in gonococcal rheumatism when the swollen joint looked angry, with severe pain and fever, indicating the commencement of suppuration. In such cases pyæmia and death might occur unless operative measures were applied in time.

In 1912 further articles on the subject were contributed by Swinburne, Kreissl, and Holliday.

Rotky (1912) described a case of fatal gonococcal polyarthritis. In the exudates of all the affected joints abundance of gonococci were demonstrated. The exudates were sero- or muco-purulent. He described the histology of the condition carefully, and found that the cartilaginous surfaces of the bones were smooth, glistening, and uninjured. The disease therefore affected only the synovial membrane of the joints. Sections of this membrane showed degeneration of the cells and formation of young granulation tissue, with a considerable exudate of polymorphonuclear leucocytes, eosinophiles, lymphocytes, erythrocytes, and a few mast cells. The inflammation affected chiefly the inner layers of the membrane, but the outer surface was also damaged. There was a proliferation of the plasma cells, with cells containing two, three, and four nuclei.

Rotky also states that the peri-articular tissues are often affected in gonorrhœal arthritis. In one case he found inflammatory changes in the muscular attachments of the joint affected.

Further papers on gonococcal arthritis have been written by Dardel (1913), Pereira (1913), and Goebel (1914).

Besson (1914) states that gonococci have been found in the pus from gonococcal joints by Petroni and Krammerer. One usually fails to find the germs in the serous fluid, since they disappear rapidly from the secreted fluid. According to Vaquez, however, the gonococcus remains for a long time alive in the articular tissues, and can frequently be cultivated from the synovial excrescences.

Chiari (1914) reviewed 470 articles published on the subject during the previous ten years. Gonococci were seldom found in the joint exudate after the acute stage was past, except in the more malignant types with involvement of the myocardium.

Stetten (1914) described a case of peri-articular suppuration of purely gonococcal origin.

Nordmann (1915) states that the smaller joints are more commonly infected with the gonococcus than the larger joints, and he maintains that gonorrhoea should always be suspected when only one joint is affected. When suspicious, examine the secretion from the vagina, uterus, urethra, etc. Other characteristics are the sudden stormy onset, extreme pain, tenderness, inability to sleep, and the failure of salicylates to give relief. He advocates hyperæmic treatment.

Prieto (1916) reports on three infants of from 5 to 20 months old with a gonococcal urethritis and multiple joint affections. The latter promptly subsided under immobilisation alone. The gonococcus was found in the urethra and vulva of these cases.

According to Luys (1917), there are four main types of gonococcal rheumatism:—

“(1) *Arthralgia*, which is characterised by articular pain only. A joint thus affected shows nothing abnormal when examined, and is in no way impaired in its mobility. The pain is most marked in the morning, when the joint is slightly stiff, but this stiffness readily diminishes as the patient gets about, and often disappears entirely during the day.

“Several joints may be affected in this fashion at the same time, or the pain may be very vague, and shift to different articulations. The character of the pain varies. Sometimes it is sharp, and shifts. On other occasions it is stationary and less intense, flaring up, however, with every recrudescence of the affection.

“(2) *Hydrarthrosis*.—This condition is most often met with in the knees, and is usually unilateral, although it may be bilateral. The synovial sac and its prolongation under the quadriceps extensor are distended, the joint is swollen, the patella is raised and separated from the long bones. This hydrarthrosis takes a very long time to disappear. It often lasts two or three months, and resists even the most energetic medical treatment. Its main feature is its stationary character, whilst the hydrarthrosis of true rheumatism is essentially a shifting one.

“(3) *Acute Arthritis*.—This is the most common form, and is characterised by violent pains affecting simultaneously several joints (two or three as a rule, seldom five or six). It is accompanied by fever, which is usually moderate, up to 102.2° F. The infected joints are extremely painful, considerably swollen, and perfectly useless. The onset is abrupt, a joint suddenly becoming painful and beginning to swell rapidly. The tumefaction follows almost immediately upon the pain, the skin becomes red, and the local temperature is raised. Acute gonorrhoeal arthritis seldom ends by resolution. Its usual termination is ankylosis.¹ Sometimes suppuration supervenes, a complication of the utmost gravity under the conditions.

“(4) *Polyarthritis deformans*.—This type of lesion is chiefly found in connection with the small joints, with those of the toes and fingers. The articulations between the first and second phalanges are often affected, and thus a curious deformity, which is typical (Fournier's radish finger), is brought about. In other cases the metacarpophalangeal joints or the big-toe joints are implicated. In all lesions of this kind atrophy of the corresponding muscles is common.”

Diagnosis.—The fact that a patient has or has previously had gonorrhoea should always arouse one's suspicions. The chief signs which distinguish it from other forms of rheumatism are the small number of joints involved, the fixed character of the condition, and the sudden inflammatory exacerbation in the affected joints, which subsides quickly. The only certain diagnosis, however, is to cultivate the gonococcus from the joint exudate. This can be accomplished in many cases by an expert bacteriologist. A positive complement-fixation test is confirmatory evidence that the patient has a gonococcal infection somewhere.

Dufour (1919) states that pressure on the intra-articular ends of the bones may be used in the differentiation of gonococcus polyarthritis from acute articular rheumatism. With gonococcus joints this pressure causes pain, but this is not so in acute rheumatism.

¹ Luys here is much too pessimistic. Many cases, under proper treatment, clear up entirely without any ankylosis.—AUTHOR.

Roentgen-ray photographs in three cases of gonococcal arthritis showed definite changes in the bones, which explained the pain on pressure. In two cases of articular rheumatism the skiagrams failed to reveal any similar changes in the bones.

The same author (1920) recalls the persistent localisation of the gonococcus in the same joint, whereas in true rheumatism the arthritis shifts about. The pain in gonococcal arthritis is also more intense than in articular rheumatism.

Roentgen-ray photographs show pronounced decalcification of the ends of the bones in a few weeks after the onset of gonorrhœal arthritis.

Treatment.—This should always be focal, local, and general. The focal treatment is directed against the focus or source of infection, and for this reason it is necessary to disinfect the urethra as rapidly as possible by means of irrigation, and to massage the prostate, the seminal vesicles, and Cowper's gland. Local treatment of the diseased joints is also important. These should be immobilised by means of splints or sandbags, etc.; and counter-irritants such as blisters, iodine, Scott's dressing, or 5 per cent guaiacol ointment often help to relieve the pain and swelling. Elastic pressure is useful to reduce the swelling, and is best obtained by wrapping the joint with loose cotton-wool and applying a bandage over the same. The pressure induced in this way over the loose cotton-wool is even and elastic in nature. Electric treatment in the form of continuous currents, or in the shape of ionisation with salicylate, is often beneficial, chiefly for the relief of pain. Hot air, steam, and diathermy are also useful and soothing. When the acute symptoms have subsided, the normal mobility of the joints should be restored by means of gentle movements and gentle massage. Wolf (1913) advocates massage in both the acute and subacute stages. While massage is undoubtedly useful in relieving the pain and swelling, and more especially in reducing the exudates at the termination of the illness, yet it is just possible that it may sometimes light up the disease by displacing latent foci of the germs, as happens in the case of tubercular joints. It should be remembered that massage is only palliative and not curative treatment. If a marked hydrarthrosis is present, compression by means of an elastic bandage, or puncture, is often useful. Bier's treatment in these cases has often given good results. Lastly, certain severe cases may require operative measures, such as arthrotomy or resection. Fuller (1909) claimed to have had good results in gonorrhœal rheumatism by vesiculotomy in the case of males.

Walther (1914) considers that surgical treatment is more successful than internal medication. He aspirates the joints and injects an antiseptic. In addition he recommends seminal vesiculotomy.

Klose (1919) states that before the Great War the incidence of gonococcal arthritis was 2 per cent. In Germany during the war the incidence was 10 per cent, due, he considers, to the improper treatment of the urethral gonorrhœa, and due also to the weakened physical condition of the patients. He states that arthrotomy was practised as a systematic treatment at the university clinic of Frankfort-on-Main. He maintains that arthrotomy is indicated if after one puncture there is a second articular effusion, accompanied by considerable stretching of the capsule, together with pain, and also when the condition of the joint indicates a commencing subluxation. The operation should also be performed in the phlegmonous and mixed types of the disease. After operation the pain promptly subsides, and the general condition begins to improve at once. In 14 per cent of the cases ankylosis was unavoidable, due to the injuries which the knee had already suffered before the arthrotomy was performed.

General Systemic Treatment.—Rasch (1916) treated 216 cases with salicylates, moist heat, and light massage. One half of these cases were cured in less than two months, and only 14 required over three months' treatment. Boas corroborated his statements as to the efficacy of this treatment, which he applied in a large number of cases, without supplementary vaccine therapy. In his opinion the results with vaccine therapy were no better than in the cases without it. In spite of Rasch's statements, there are many who believe that salicylates are of little value; *vide* Fuller (1909). Indeed, some use

sodium salicylate as a diagnostic agent, whereby, if no relief is obtained from the drug, the gonorrhœal nature of the disease is suspected. Certain other drugs, such as injections of colloidal silver (electrargol, collosol argentum, etc.), colloidal iodine, colloidal sulphur, etc., have been given with uncertain results; *vide* also McDonagh's colloidal preparations, Chapter XXXIV.

Vaccine Therapy.—There can be no doubt whatsoever that this is the most reliable form of treatment which we possess for gonorrhœal rheumatism. In the chapter on vaccine therapy it will be noted that 99 per cent of the hundreds of authors who have written on the vaccine treatment of gonorrhœal rheumatism declare that gonococcal vaccine is of very great value in this complication of the disease. Full details of the various methods of administering this vaccine will be found in Chapters XXX., XXXI., and XXXII.

The author has had very excellent results with detoxicated gonococcal vaccine (*vide* Chapter XXXI.). Many cases clear up in three weeks or even much more quickly with this treatment alone.

Serum Therapy.—*Vide* Chapter XXXIII.

Muscular Rheumatism due to Gonorrhœa.—During an attack of gonorrhœa it is quite common to get pains in the muscles of the loins, neck, back, arms, and legs. It would appear that these are somehow connected with the gonococcal infection; but whether they are due to the germs actually circulating in the system, or to their toxins, we are at present unable to state. It is quite possible that they are due to the circulating toxins, as large doses of gonococcal vaccine sometimes give rise to similar pains.

Gonococcal Suppurative Myositis.—Harris and Haskill (1904) described a case of this rare affection in a woman with leucorrhœa but no history of gonorrhœa. She developed a swelling in the sacral region and also in the calf, from which pus was evacuated. Sloughing of the muscles occurred. Gonococci were found in the pus microscopically and culturally. They state that all previous recorded cases of myositis were considered to be due to the toxins of the gonococcus.

Gonorrhœal Synovitis and Bursitis.—One often finds gonorrhœal metastases in the tendon sheaths as well as in the joints, and more rarely the bursæ are affected. Jundell and Ahmann (1897), Griffon and Nattan Larrier (1901), were able to cultivate the gonococcus from such conditions, thereby definitely establishing the etiology. The latter observers recorded a case in which the bursa of the tensor fasciæ femoris muscle was inflamed. Puncture yielded a distinctly purulent fluid, in which the direct examination and cultures on blood agar showed the presence of gonococci. When a second puncture was made twenty-four hours later, no more diplococci were found in the pus, but the culture gave a positive result. Lastly, the material obtained from a third puncture a few days later showed no gonococci under the microscope or in cultures.

These observations are interesting in so far as they prove how easily the gonococcal nature of such affections can be overlooked, unless the bacteriological examination be made immediately.

Meyer (1903) described a case of gonorrhœal whitlow of the tendon sheath of a finger in which he obtained cultural proof.

Hocheisen (1906) was able to cultivate gonococci from the purulent exudate in the tendon sheaths of an infant which was born with gonorrhœal ophthalmia. The tendon sheaths were in this case affected simultaneously with the joints.

Fiske (1910) communicated a paper on the invasion of the gonococcus into bones, joints, tendons, and bursæ.

According to Luys (1917) the tendon sheaths most commonly affected are those in connection with the peronei muscles of the leg, the extensors of the toes and of the fingers, the muscles of the thumb, the radiales, the flexors of the fingers, the semi-tendinosus and the semi-membranosus.

Thus gonorrhœal synovitis is chiefly found in the feet, the ankle, the knees, and the wrists—that is to say, in the regions of those joints which are most often affected by gonorrhœal rheumatism. These lesions are characterised by a swelling and a reddening of the integuments along the course of the tendon sheath. The spontaneous or provoked pain is very marked, and the voluntary movements are difficult or impossible.

Luys states that bursitis is less common than synovitis. The retro- and subcalcaneal bursæ are the most commonly involved. The pain in the heel (talalgia), which is so frequently observed during an attack of gonorrhœa, is sometimes due to inflammation of these bursæ, but more often it is due to osteitis and exostosis of the os calcis.

Gonococcal Affections of the Nervous System.—Severe affections of the nervous system due to the gonococcus have been recorded, and may be regarded as genuine, in spite of the fact that absolute proof is lacking.

Kucharczewsky (1900) observed polyneuritis, and Batut (1901) described a gonococcal sciatica.

According to Luys (1917), gonorrhœal sciatica is the most important of all the forms of neuralgia met with in gonorrhœa. Professor Fournier studied the condition carefully, and demonstrated its gonococcal nature. Its onset occurs usually during the second and third month of the gonococcal invasion. It is sudden, and lasts three to four days as a rule, and is very seldom present for more than fifteen to twenty days. It is most amenable to treatment, and often vanishes as soon as one manages to subdue the discharge.

Kankarowitsch (1902) recorded a case of general systemic gonorrhœal infection, in which there developed paralysis of all the limbs with secondary atrophy of the muscles.

Cases of acute myelitis as complications of acute gonorrhœa have been described by Hayem and Parmentier (1888), Dufour (1889), v. Leyden (1892), Engel-Reimers (1892), Barié (1894), v. Rad (1900), Block (1905), Debove (1905), and Kölichen.

Nerve paralysis cases resulting from gonorrhœa have also been noted by Lazarus (1896), Nürnberger (1904), and Bernhardt (1905). Boissonas (1905) recorded a case of chorea in a little girl suffering from gonococcal vulvo-vaginitis. The chorea disappeared as soon as the gonorrhœa was cured.

According to Eulenburg (1900), there can be distinguished three principal types of localised gonococcal affections of the nervous system:—

- (1) Neuralgic affections, especially sciatica.
- (2) Muscular atrophy and atrophic paralysis.
- (3) Neuritis and myelitis.

According to Luys (1917), the meningo-medullary complications of gonorrhœa are rare. They usually supervene about the third or fourth week of the disease.

More or less severe pain in the lumbar region, accompanied by girdle pains, is noted. The most characteristic symptom, however, is paraplegia, which usually comes on gradually, but occasionally it is complete at the onset. Retention of urine and constipation, or the reverse, incontinence of urine and fæces, are met with.

The knee jerks are usually exaggerated, but they may be diminished or absent. Ankle clonus is also sometimes present.

Muscular atrophy has been noted repeatedly, and when present to a marked degree is of serious import. Marcel Labbé (1901) published a case in which there was marked muscular atrophy in the leg and thigh, with exaggerated reflexes.

Luys observed in 1910, in a youth with gonorrhœal vesiculitis, symptoms of spinal irritation, viz. exaggerated knee jerks, ankle clonus, and retention of urine. His pupils were also widely dilated. The condition cleared up with irrigation of the urethra and massage of the vesicles.

He further states that cases of gonococcal paraplegia are generally spastic, and accompanied by slight sphincter troubles and considerable muscular atrophy. They

usually coincide with a mild attack of rheumatism, and are slight and curable as a rule. The prognosis is favourable, and recovery generally takes place within a few months or a year. Sulphur baths, massage, and electric treatment of the muscles are of great value. Treatment of the urethra and its appendages is also important, as well as appropriate symptomatic treatment of the various manifestations of the myelitis.

Luys thinks it is probable that the gonococcal toxins alter the cells of the spinal cord and produce foci of myelitis, traces of which have been found at the post-mortem in a few instances. Although in all the above-mentioned nervous affections it was never demonstrated with certainty by cultures or smears that the gonococcus was the direct cause of the malady, yet it is nevertheless probable that these conditions were really due to a true gonococcal metastasis. We must, however, consider another possibility, viz. that the nervous system may have been affected by the circulating toxins of the germ. Von Wassermann and Moltschanoff injected gonococcal toxin into mice, and produced thereby paresis and lameness of the extremities. Histological examination of these animals revealed changes in the cells of the roots of the spinal nerves and of the posterior columns of the spinal cord. These researches have not yet been confirmed by others.

Again, certain cases of gonococcal neuritis may only represent referred pains from the inflammatory processes in gonococcal arthritis or prostatitis, etc.

Bieck (1907) published a case of gonococcal meningitis in a man of 48 who had been suffering from gonorrhœa for a year. Six days after an exacerbation of his urethral discharge he became maniacal, and coma and death followed shortly afterwards. At the autopsy exudative patches were found on the cerebral pia mater, especially in the regions of the right frontal and parietal lobes. The microscopic examination of these exudates revealed the presence of the gonococcus.

Josselin de Jong (quoted by Besson, 1914) found the gonococcus in the cerebro-spinal fluid of a young man affected with cerebro-spinal meningitis at the end of an attack of urethral gonorrhœa.

Aaser and Holst (1918) point out that a gonococcus general infection may occur without urethritis, and, *vice versa*, a meningococcus general infection may occur without meningitis. In some sporadic cases of meningitis the organism which they found seemed to resemble more the gonococcus than the meningococcus.

Boivin (1919) described a case of meningitis associated with gonorrhœa. The patient, who had contracted gonorrhœal urethritis about four weeks previously, and who was at the time suffering from orchitis, developed symptoms of meningitis, but recovered after a month in hospital. The fluid removed by lumbar puncture was purulent, and contained almost exclusively polymorphonuclear cells which did not show any signs of degeneration. No bacteria of any kind could be found on microscopic examination, and all attempts at culture from the pus gave negative results. As convalescence set in, the cell content of the spinal fluid became altered, the cell count showing 85 per cent of mononuclear cells and only 15 per cent of polymorphonuclear cells. It is noted that the patient had suffered from epidemic cerebro-spinal meningitis some four years previously.

Smith (1922) has described a fatal case of gonococcal meningitis occurring suddenly in a patient under treatment for acute gonococcal urethritis. Smears and cultures from the cerebro-spinal fluid were both positive. The cultures showed true gonococcus colonies, and the identity of the germ was proved by serum and fermentation tests.

Larkin and Jelliffe (1913) described a case of acute infective encephalitis which they believed to be of gonococcic origin. The patient had a gonococcal infection of the posterior urethra. After death a smear from the brain showed Gram-negative cocci, and a culture on serum-agar produced colonies corresponding in character with the gonococcus.

Ortali (1914) reported on a case of sclerosis of the corpus callosum of gonorrhœal origin.

According to Luys (1917), the cerebral complications of gonorrhœa are more obscure than those of the spinal cord.

Gonorrhœal delirium has been described by Bourdon (1868) and Bonnet (1877). Vidar (1875) described gonorrhœal insanity and also apoplexy. The evidence produced, however, is not absolutely conclusive.

Gallavardin and Delachanal (1912) recorded a case of angio-neurotic œdema occurring during an attack of gonorrhœa.

Gonorrhœal Affections of the Skin.—Gonorrhœal skin lesions are chiefly found in men, and are usually noticed about the fourth or fifth week of the disease. A large number of cases have been described in the literature. The condition apparently may assume different types, such as simple erythema, urticarial, papular, and vesicular eruptions, purpura, and finally hyperkeratosis. These skin conditions may be regarded as due to a genuine gonococcal metastasis, as this is borne out by the observations of Scholtz (1903), who was able to cultivate gonococci from two suppurating papules in an exanthematous patient. Paulsen (1905) found Gram-negative diplococci in the skin papules of an eruption which followed after an attack of gonococcal ophthalmia. Baginsky (1903) also found the gonococcus in an umbilical ulcer of a boy suffering from gonorrhœa. On the other hand, Buschke (1899) and others believe that certain skin affections, such as hyperkeratosis, are due, not to the gonococcus itself, but to its circulating toxins. He divided the skin conditions into two principal groups:—

(1) Folliculitis, ulceration, and abscesses.

(2) Gonorrhœal exanthemata, the most common being simple erythema with vesiculation.

(1) **Erythemata.**—This condition sometimes simulates measles or scarlet fever.

Löhe reported a case of marked herpetiform exanthema, with a coloured plate.

Buschke pointed out the danger of confounding the condition with drug exanthemata, *e.g.* due to balsams.

In 1905 the Director-General of the Medical Department of the Admiralty described two cases of gonorrhœa in which a rash very like scarlet fever developed over the whole trunk, arms, and thighs, and partly on the neck. This rash faded in four to seven days. No drugs had been given to account for the condition.

Luys cites a case described by Hodara (1912) wherein a soldier on the third day of his urethral infection was admitted to hospital with an eruption on his chest, face, arms, and legs. This eruption was composed of rounded and polymorphous erythematous patches. He had fever (102.9° F.), and within forty-eight hours the erythema had become general, and assumed a bullous character. The various bullæ were filled with a purulent liquid, which in some instances was blood-stained. His face, which was remarkably red, became œdematous, and conjunctivitis supervened. Gradually the various patches underwent desquamation, and the bullæ were superseded by scabs. The fever remained at 102° F. for eleven days, and the patient was very depressed and feeble. The nature of the complaint remained obscure for a week, until cultures were made from the blood which revealed the presence of the gonococcus.

(2) **Purpura.**—Luys (1917) states that this condition chiefly occurs on the lower limbs, and seldom spreads above the knees. It is also met with on the mucous surfaces, on the arch of the palate, and in the larynx. General malaise and other systemic disturbances usually accompany gonococcal purpura, and suggest typhoid fever. The duration of the eruption is very variable, from twenty-four hours to three, four, or ten days according to the case. The diagnosis is often difficult. He describes a case of resistant urethral gonorrhœa which suddenly developed the condition, and which had been diagnosed as a syphilitic roseola, although the patient had never had any trace of syphilis. No drug capable of causing a rash, such as copaiba, had been administered, and he considered that it was one of the rare manifestations of gonorrhœa.

(3) **Hyperkeratosis.**—According to Luys, Vidal (1893) was the first to draw attention

to this gonococcal affection of the skin, which since then has been described under the name of "corne cutanée" by Jeanselme (1895), as well as by Jacquet and Robert, and also by Chauffard.

This skin disease usually appears some three to five weeks after the beginning of the gonorrhoeal attack, and is almost exclusively found in cases which present serious complications. The first manifestations are usually small, reddish vesicles. Later these become more or less pronounced horny crusts. They spread and coalesce and form hard, irregular patches, composed of epidermic horny masses. As a rule these hyperkeratinised areas are remarkably symmetrical. They are chiefly found on the limbs, especially on the palmar surfaces of the hands and on the soles of the feet. Eventually they come away as thick horny casts, and the nails usually come away with them. This keratinisation, however, may occur anywhere on the legs and around the knees, on the arms, and even on the face, on the scalp, and on the genitals.

Jeanselme favoured the view that the condition was due to the toxins of the gonococcus acting either directly on the skin or indirectly through the nervous system, thereby producing trophic changes. In support of this opinion he found that the reflexes in the lower limbs were greatly exaggerated, and the condition improved rapidly with the general progress of the patient.

According to Chauffard, the disease is due to an exalted and cachexia-producing virulence of the gonococcal infection, which leads to trophic disturbances. The lesions remain stationary for a very long time, and often recur if the patient is unfortunate enough to get a fresh attack of gonorrhoea.

Arning (1911) found 23 cases of gonococcal hyperkeratosis reported in the literature. Since then many more cases have been described.

Sequeira and Turnbull (1910) were apparently the first to describe an authentic case of this malady in Britain.

Williams (1910) described a case in which the hands and feet were involved. He declared that the condition was very rare, and only occurred in cases in which there was other evidence of gonococcal septicæmia, such as arthritis, etc. Two forms of the disease occurred, either together or separately. (1) A diffuse thickening of the horny layers of the skin; (2) isolated horny cones or domes, mostly on the hands and feet, but sometimes in other places. In his case no gonococci were found in cultures made from the greyish, putty-like material found under some of the horny masses.

Heerfordt (1910) maintained that sub-epidermoid vesicles frequently developed in the course of a superficial dermatitis, and the vesicles may be grouped to resemble herpes, even without any preceding dermatitis. According to this author, these gonorrhoeal skin affections frequently display a hæmorrhagic tendency, and the dermatitis is sometimes accompanied or introduced by rheumatoid pains, suggesting involvement of the peripheral nerves. He drew a comparison between the phlyctenular or herpetiform character of the lesions in the skin and those which occurred rarely in metastatic affections of the cornea. In 537 cases of gonorrhoea in women he found record of herpes outside the genital region in 7 cases, and in 10 cases out of 1773 men. The proportion was in all probability larger, as only the severer forms of herpes were recorded. He reviewed the literature on the subject, adding that both the ocular and the cutaneous herpetiform manifestations were generally mild and comparatively transient.

Pugh (1912) wrote an article on the skin complications of gonorrhoea. The author has unfortunately been unable to gain access to his paper.

Haslund (1913) reported on a case of generalised gonococcal infection with keratosis. The patient, a man aged 37, suffered from a recurring gonococcal urethritis. He developed reddish pin-head spots scattered over his hands, then vesicles formed. Some of these suppurated and others dried up. Later, small papules developed on the legs and body, and patches developed on the penis, resembling psoriasis. The cutaneous affection as well as the urethritis subsided for a year, after which time it flared up again for two months.

Staphylococci were isolated from the confluent vesicles. The condition again subsided, but returned a few months later, accompanied by a relapse of the urethritis. The Wassermann test was negative. Most of the time the patient had a subacute arthritis, without ankylosis, and also an endogenous conjunctivitis.

Haslund states that keratosis generally develops as a "balanitis hyperkeratotica." More rarely it involves the hands and feet, and only exceptionally other parts of the body. The keratosis passes first through a vesicular stage, and this is followed by a hard crust formation. The affection may also blend into other forms of gonorrhoeal exanthemata.

Selenew (1913) described a case of gonorrhoeal keratosis of the soles of the feet, accompanied by muscular rheumatism, arthritis, and muscular atrophy.

Diernfellner (1914) contributed a paper on gonorrhoeal skin eruptions.

Sanfilippo (1915) reported on a case of gonorrhoeal keratosis of the penis. The patient was suffering from acute gonorrhoea with involvement of one knee, when circinated keratotic lesions developed on the penis, commencing around the urinary meatus. The lesions showed the characteristic horny patches, and all subsided as the gonorrhoea yielded to treatment, thus confirming the gonorrhoeal nature of the affection. It was the patient's second attack of gonorrhoea after an interval of five years.

Brown and Davidson (1917) had a patient with gonorrhoeal hyperkeratosis, which they claim to have been the sixth case reported in Britain. The condition was complicated with arthritis. Cultures from the affected joints and from the diseased skin remained sterile.

Woodward (1918) maintained that only two previous cases of gonorrhoeal keratoderma (hyperkeratosis) had been recorded in Britain, one by Sequeira and one by Graham Little (no references given). He has overestimated, however, the rarity of the condition, since there have been more accounts in the British literature than he imagined.

Woodward's patient (a male) had a gonorrhoeal history of six years' duration. Gonococci were found in the urethral discharge. He developed arthritis, with a temperature of 99° to 103° F., upon which salicylates had no effect. Six weeks after admission the skin condition manifested itself, commencing between the toes and fingers. It spread over the feet and over the fingers to the wrists in patches resembling oyster shells in size and appearance. Small dark brown patches also appeared on the lower part of the legs and over the elbow joints. Subsequently small patches also appeared on the face. The terminal ends of the palmar surface of the fingers and of the plantar surface of the toes became horny, and some of the nails dropped off. The wrists, fingers, and toes became much distorted, and there was considerable pain in the joints and marked general wasting. The patient was scarcely able to move a muscle, and was unable to feed himself.

No gonococci were found in the diseased skin, but streptococci, apparently a secondary infection, were found.

The patient improved steadily on small doses of gonococcal vaccine (4 millions), combined with an autogenous streptococcal vaccine. He slowly recovered the use of his muscles and was able to walk. A certain amount of stiffness and distortion of the joints, however, remained.

Woodward considers that the condition was due to a gonococcal toxæmia. The Wassermann reaction was negative, and there was no history of syphilis.

Laing (1919) described a case of gonococcal keratosis resembling in some respects secondary syphilis. Twenty-one days after the commencement of the gonococcal infection pain developed in the right knee, and then both knees and ankles became swollen. Seventeen days after the onset of the arthritis, small moist papules appeared on the coronal sulcus of the penis and around the anus, like condylomata. Lesions also occurred on the mucous membrane of the lips and cheeks, oval in outline and bluish-pink in colour, resembling mucous patches. (The Wassermann test, however, was negative.) Next day small nodular bullæ appeared on the soles of the feet and on the legs. They were quite isolated, and when a few days old they formed a horny mass of a dark brown colour. This

also occurred on the shins, thighs, and over the abdomen and chest wall. A few also appeared on the hands and arms. The condition was treated with injections of intramine, with apparent success.

Strandberg and Hedenius (1919) describe a case of fatal gonococcal arthritis with keratoderma in a young man. The skin condition did not develop until two years after the commencement of the gonorrhœa. The malignant course of the slow chronic arthritis and the extraordinary changes in the skin were the striking features of this case. Not the slightest benefit was derived from salicylic treatment or that for syphilis, and death occurred from a general cachexia.

The spleen was enlarged, but the blood was relatively normal. The skin lesions were of the hyperkeratosis type or parakeratosis. He considers it possible that a secondary post-gonorrhœal infection may favour the development of the skin lesions, and states that there is still no decisive evidence to prove that this parakeratosis is due to the gonococcus.

Lees (1922) has described two cases of this malady illustrated by photographs of the condition.

It would appear that gonorrhœal hyperkeratosis or keratoderma is not quite so rare as was formerly supposed. In 1918 the author saw three severe cases in Dr. Allport's clinic at the Military Hospital, Rochester Row. These resembled the case described above by Woodward, in that there was extreme wasting, pain, and inability to move the arms and legs. Apparently, however, they were even more severe than Woodward's case, since the whole of the skin and nails of the hands and feet came away as hard, horny casts. Dr. Allport had quite a collection of these casts, as shown in Plate XVIII. Similar less severe cases occurred in Dr. Armstrong's clinic at the same hospital. The author tried very hard to cultivate gonococci from the cheesy material under the hard, horny skin of these cases, but always failed, due perhaps to the fact that many of them were heavily infected with secondary organisms such as diphtheroid bacilli, staphylococci, and Gram-negative bacilli. In smears from one of the very severe cases there were found masses of Gram-negative diplococci resembling gonococci, but definite proof was lacking, due to failure to grow them in the culture tube. The severe cases eventually recovered after a long illness.

It is quite evident from the above literature that this complication is practically always accompanied by arthritis. In other words, it is due to a metastatic gonococcal infection. Whether or not, however, the gonococci actually attack the skin, or whether it is due to a toxæmia causing atrophic nerve disturbances, still remains to be proved.

Gonococcal Metastatic Nephritis.—This is apparently a very rare complication, and no definitely proved case has ever been recorded so far as the writer knows. Hæmorrhagic nephritis has been observed by several authors in certain cases of general gonococcal infection, especially following upon gonorrhœal endocarditis. Honl (1899) casually stated that a toxic hæmorrhagic nephritis was often found in gonococcal endocarditis cases. Most of the published cases, however, are doubtful, since the evidence was only clinical, without bacteriological or pathological proof. Rotky (1912) examined the literature on the subject, and pointed out that in the cases reported by Brecht (1889), Neuendorff (1892), Ahmann (1897), Schmidt, E. (1897), Lewis (1900), Wladimirsky (1902), Selkei and Unterberg (1907), and Löhlein (1910), no histological sections had been made, and he concluded that there was no definite proof in any of these cases to show that the condition was caused directly by the gonococcus. Rotky described a hæmorrhagic condition of the kidneys in a fatal case of gonococcal systemic infection in one of his own patients. Sections of this case showed a diffuse hæmorrhagic nephritis, with hæmorrhagic proliferative glomerulitis. The interstitial tissues were swollen and infiltrated with leucocytes (plasma cells and lymphocytes). According to Schridde (1910) the occurrence of plasma cells is quite characteristic of subacute and chronic gonorrhœal affections; but according to Rotky plasma cells also occur in scarlatinal nephritis, and in various other forms of acute and subacute inflammations of this organ.

PLATE XVIII



No. 1.—Gonococcal pustules in the skin of the penis, in a case where the urethra was not infected.



No. 2.—Hard, horny casts which came away from the feet of Dr. Allport's keratoderma cases.

He was able to find Gram-negative diplococci in the kidneys of this case, but did not definitely prove that these were gonococci, since the cultures made from the kidney substance remained sterile. Löffler's medium was used, and he considers that this may explain why no growth occurred, since it is not very suitable for the gonococcus. Anyhow, the fact that the culture tube remained sterile showed that other pyogenic organisms were not implicated. Rotky believed that the nephritis was due to the gonococcus itself, or else it might be considered as a toxic hæmorrhagic diffuse nephritis resulting from a severe systemic gonococcal infection. The germ was cultivated from several of the joints in this case.

Hagner (1910) reported a case of gonococcus infection of the kidney.

Simmons (1922) cites the case of a man who entered hospital with violent pain in the right side of the abdomen. He had had gonorrhœa four months previously. The day prior to admission he had been struck on the abdomen with a lump of coal. This gave him severe pain in the abdomen, and he had to stop work and go to bed. There was nausea, but no vomiting. An exploratory laparotomy was done, and rupture of the right kidney was found. The capsule was opened and about 8 ozs. of a thin, blood-stained, purulent fluid was expressed. A portion of this fluid was kept for laboratory examination. From direct smears without sedimentation large numbers of intra- and extracellular Gram-negative biscuit-shaped diplococci were demonstrated. A pure culture of the gonococcus was also obtained on one per cent glucose-ascitic fluid agar.

Gonorrhœal Metastatic (or Endogenous) Inflammation of the Eye.—(1) **Conjunctivitis.**—Besides the recognised gonorrhœal conjunctivitis due to direct contact infection, there also occurs rarely a true metastatic conjunctivitis as a result of gonorrhœa. Van Moll read a paper in Utrecht in 1899 entitled "Is there a Metastatic Conjunctivitis?" Later, Lesser (1902), Kurka (1902), Paul (1905), Greeff (1905), and Haltenhoff also described the condition. Zum Busch (1906) described a case of what he called "gonotoxic" ophthalmia, in which no gonococci could be found in the discharge from the eye, although many were found in the urethral discharge.

Murray (1910) reported on a case occurring in the course of a gonorrhœal attack complicated with arthritis. Microscopic examinations made frequently throughout the attack failed to reveal the presence of gonococci in the conjunctival secretion. The condition was bilateral. There was a moderate amount of discharge, with slight swelling of the lids and chemosis of the bulbar conjunctiva. The disease ran a mild course, but tended to recur.

Sidler-Hugenin (1912) also reported on this condition.

According to Pincus (1914) the occurrence of metastatic or endogenous gonorrhœal conjunctivitis is now universally recognised, although views differ as to its frequency and rarity. In the *Handbuch der Augenheilkunde* both Groenouw and Saemisch discuss metastatic conjunctivitis in gonorrhœa very fully, and Elschmig in the *Handbuch der Geschlechtskrankheiten* acknowledges, in spite of scepticism, the occurrence of the clinical picture of a metastatic conjunctivitis. Heerfordt out of 2300 cases of gonococcal urethritis found 23 cases of metastatic conjunctivitis. They occurred principally in the bulbar conjunctiva, and developed under the conjunctival surface, often with the formation of phlyctenulæ, so he called the condition "subconjunctivitis epibulbaris gonorrhœica." His description coincides with that of Elschmig, but Groenouw and Saemisch mention the prevalence of involvement of the fornix.

Pincus describes a case in which the fornix was involved and which remained unilateral, a very rare occurrence according to all authors. The patient had a gonococcal urethritis and vaginitis for several months, and woke in the morning with an inflammation of her right eye. Examination showed slight swelling of the lower lid and a small amount of muco-purulent discharge between the lids at the inner angle of the eye. The conjunctiva of the lower lid was very much congested, and the lower fornix was markedly oedematous. The swelling extended from the outer canthus to the swollen and hyperæmic

caruncle. There was therefore a circumscribed œdema or serous effusion into the lower fornix; the remainder of the conjunctiva above was normal. On the next day the symptoms had improved considerably, but a very painful exudative inflammation of the left ankle joint developed overnight. On the fourth day the eye was entirely normal. The conjunctival discharge was examined repeatedly without finding a single gonococcus, whereas the findings in the vaginal and urethral secretions were positive. Elschmig considers that definitely proved cases belong to the greatest rarities.

Péchin (1917), in Luys' text-book on gonorrhœa, states that metastatic gonococcal conjunctivitis is really an inflammation of the conjunctival epibulbar connective tissue (mucosa, submucosa, and episclerotic). In contradistinction to the ordinary infective gonococcal ophthalmia, the metastatic form is mild in its symptoms and the prognosis is good. The eye is more or less red and hyperæmic. The bulbar conjunctiva is slightly raised by a serous chemosis, but there is no discharge. The eye is not closed; there is no photophobia and no pain. The condition lasts about ten to twenty days, and then disappears without leaving a trace. The vision remains perfect, and the cornea is never affected to any extent. At the most a few phlyctenules may be found. This conjunctivitis owes its origin to a generalised gonococcal infection, and as a rule occurs along with an arthritis. It may precede, accompany, or follow the joint trouble. It has the same shifting character as the gonococcal articular affections. It may pass from one eye to the other, and disappears and recurs.

In this metastatic affection the presence of gonococci has rarely, if ever, been proved. Péchin states that the germ has exceptionally been found associated with staphylococci. The prognosis is favourable, provided the inflammation remains limited to the conjunctiva.

(2) **Endogenous Corneal Affections.**—Coleman described a case of relapsing corneal disease with gonococcal arthritis.

Apetz (1903) reported on an exceptional case, since it showed large corneal ulcerations with purulent infiltration and exudation into the anterior chamber. Evidently this case was complicated with a mixed infection. He cited a similar case observed by Martin.

Posey (1907) reported on this condition, but the nature of the disease in his case was doubted in the discussion which followed.

Groenouw and Elschmig do not believe that a causal connection between gonorrhœa and corneal disease (keratitis) has been proved.

Heerfordt (1910) described a number of cases, with beautiful illustrations. He observed corneal keratitis in 8 out of 23 cases of gonorrhœal epibulbar subconjunctivitis, and also in a few other cases. This phlyctenular, herpetiform, or parenchymatous keratitis complicating the gonorrhœal subconjunctivitis was, in his opinion, of endogenous origin. He gave a plate of the ocular findings in 12 cases to illustrate the various types mentioned. These cases showed characteristic epithelial elevation, with phlyctenula or vesicle formation. He distinguished between (a) vesicular, (b) parenchymo-vesicular, and (c) parenchymatous forms. He further assumed that corneal keratitis was always secondary to a gonorrhœal metastatic subconjunctivitis.

Heerfordt, further, draws a parallel between the corneal condition and the skin affections in gonorrhœa.

Pincus (1914) agrees with Heerfordt that metastatic gonococcal conjunctivitis is very uncommon, and that corneal keratitis is a very unusual complication. Moreover, the difficulties in proving its gonorrhœal origin are very great. He points out that: (1) Scrofulosis must be excluded. (2) Gonococci must be demonstrated in the discharge from the urethra or vagina. (3) There must be manifestations of a systemic infection in the joints, etc. (4) If conjunctivitis is present, an examination of the conjunctival secretion must be negative for gonococci, in order to exclude the possibility of an external infection.

He describes two cases. The first had an attack of gonorrhœa of ten years' duration, with joint complications, and gonococci were still present in the urethra. No gonococci were found in the conjunctival secretion in many examinations. In the cornea there was a row of small, superficial, rounded opacities. Later, the patient had a recurrence of joint trouble and urethritis, in the course of which there developed an iritis.

The second case had gonorrhœa twenty years previously, followed by rheumatism, which lasted several years. Seventeen years later the patient developed iritis, first in the right and then in the left eye, which lasted five months. Later, corneal keratitis developed.

Pincus points out that in both of these cases all the requirements for a gonorrhœal diagnosis are complied with. The corneal condition in both was characteristic. It was purely epithelial in nature, indicating a vesicular origin. The onset was rapid. It spread rapidly and healed rapidly.

Unlike Heerfordt's cases, the condition occurred independently of conjunctivitis. He disagrees further with this author, who believed that parenchymatous clouding was the primary condition, and epithelial elevation secondary. Pincus believed that the condition was primarily a vesicular elevation of the epithelium, or, in other words, a kind of herpes due to the gonococcus or its toxins.

(3) **Gonococcal Metastatic Infection of the Uveal Tract—Iritis and Chorioiditis.**—Numerous clinical observations—*vide* Greeff (1901), Griffith (1901), Markheim (1902), Apetz (1903), Lehmann (1905), Lapersonne (1905), Ullmann (1905), Burnett, Baylac, and Galezowski (1905)—all point to the fact that the condition of iritis, irido-chorioiditis, and cyclitis may arise due to a genuine gonorrhœal metastasis. The bacteriological proof, however, is very difficult, and up to the present gonococci have never been demonstrated by smear or culture in such affections.

Giani (1906), Stephenson and Rosa Ford (1906), Posey (1907), and McEttles (1907) have all reported on cases of metastatic gonorrhœal iritis. The latter observer terms the condition a "para-gonorrhœal" affection, and considers that it is caused by the toxins of the germs. No gonococci were ever found in the eyes after a careful search, but they were plentiful in the urethral discharge.

Baylac, and also Galezowski, did not believe that the gonococcus was actually present in the iritic lesions, but that the toxins were the cause. They noticed that the condition was usually associated with a posterior urethritis, and generally with an arthritis as well.

Beaumont (1908) quotes from Griffith (1901), who gave a series of cases in which the iritis did not follow the gonorrhœa until after the expiry of from four to fifteen years. He considers that gonorrhœa is a disease as constitutional and as difficult to eradicate as syphilis, and points out the sequence of events, namely, gonorrhœal urethritis, arthritis, and iritis. Sixteen out of 20 cases of iritis which came under Beaumont's notice confessed to gonorrhœa.

Shumway (1910), and Harrell (1913) wrote further communications on the subject, and La Motte (1915) reported a case of metastatic gonococcal kerato-iritis.

Herbert (1912) maintained that gonococcal iritis was a recurrent disease, existing until the focus in the posterior urethra was eradicated.

Vandegrift (1912) reported on a case of metastatic chorioiditis occurring in an old relapsing case of gonorrhœa. The complement-fixation test was positive, and the condition was cured by treatment with gonococcal vaccine. He states that the possibility of the chorioid becoming metastatically affected from the urethra as a sequel to arthritis was suggested by De Schweinitz (1906).

Péchin (1917), in Lays' text-book, states that the iris may be implicated alone (plastic iritis, or purulent iritis with hypopyon or hæmorrhagic iritis), or so-called "serous iritis" may be present, in which the whole uveal tract is involved. He further states that it is not generally well known that metastatic chorioiditis has often been observed in cases of systemic gonorrhœal infections. The condition occasionally supervenes at

a very remote period, two, three, and even twenty-five years after the original infection. It was always caused by a gonococcal infection of the genito-urinary organs which had not been cured, and which had remained latent for years. As the usual signs of chronic gonorrhœa were absent, a methodical examination of the genito-urinary organs was the only available means of tracing the true origin of the ocular affection.¹

Cobbledick (1918) found that in a series of 9 cases of recurrent "rheumatic iridocyclitis" the gonococcus was present in the genito-urinary tract in every one, after periods of from seven to thirty years since the last infection. More recent work has confirmed his belief in the connection between the two diseases, and in the chronicity of prostatic infection by the gonococcus. For the discovery of the gonococcus, massage of the prostate and examination of the centrifugalised urine within four to six hours of the collection of the specimen are insisted upon. The connection between iridocyclitis and the gonorrhœa is considered to be proved by (1) the consistency of the association, (2) the improvement after treatment with gonococcal vaccine, and (3) the reaction of the eye to the injection of the vaccine. The aqueous humour has not been examined for the gonococcus, but the writer suggests that this should be done in view of the successful demonstration by Mayou and Hancock of staphylococci in cases of septic iridocyclitis.

He described a severe case which led to the loss of the left eye. The focus in this patient proved to be the seminal vesicles. The gonococci reached the eye through the blood stream. In the case of the retina, they are conveyed by the arteria centralis retinae; the uvea is reached through the long ciliary vessels. They travel to the iris through the anterior ciliary arteries, and to the chorioid through the short posterior ciliary vessels.

(4) **Optic Neuritis.**—According to Péchin (1917), metastatic optic neuritis belongs to the same type as the gonococcal polyneuritis and the cerebro-spinal lesions. In the same way as the gonorrhœal infection reaches the cord through the arteries or veins, the optic nerve is affected through the blood stream. This optic neuritis is an infective neuritis, and the cord or even the brain may be involved.

Other gonococcal lesions of the eye which deserve to be mentioned are :—

- (1) Tenonitis (inflammation of the Tenon's capsule).
- (2) Thrombo-phlebitis of the central vein of the retina.
- (3) Dacryo-adenitis.

Treatment of the Ophthalmic Lesions in Gonorrhœa.—Local treatment of these metastatic conditions is often powerless. It is of great importance to treat the primary gonococcal focus in the urethra, prostate, or vesicles. In addition, many observers have had good results with vaccine treatment. The local measures necessary with regard to the eyes are described in text-books which deal with diseases of the eye.

Other Conditions of supposed Gonorrhœal Origin.—Grekow (1912) states that he has encountered a number of cases of perigastritis in which the infection originated in the genital organs, and was of a gonococcal or other nature. Adhesions occurred about the pylorus, also between the adnexa and the omentum. As a rule the condition was accompanied by motor insufficiency of the stomach. In one case the patient began to vomit constantly after the gonorrhœal genital affection had lasted for some time.

Solowij (1913) reported on a case of rupture of the uterus during delivery, the cause of which he attributed to gonorrhœa.

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¹ The presence of gonorrhœa can now be detected by the complement-fixation test. The writer has often obtained strongly positive reactions in cases of iritis where apparently no other signs of gonorrhœa were present.

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CHAPTER XXIV

BALANITIS

By Dr. ROBERT THOMSON, M.B., Ch.B., Edin.

Balano-posthitis.—An inflammation of the mucous membrane covering the glans penis is called *Balanitis*, while an inflammation affecting the mucous membrane of the prepuce is called *Posthitis*. However, as the inflammation mostly affects both surfaces simultaneously, the condition should be considered as one, under the term *Balano-posthitis*.

The condition is practically always caused by a tight or long foreskin—phimosis, owing to the accumulation of smegma and secondary organisms within the preputial sac. It is frequently seen as a complication of chancre, chancroid, and gonorrhœa, also in gouty and diabetic patients, when the person affected has phimosis.

Symptoms.—There is a marked sensation of heat and itching referred to the point of the penis. The mucous membrane is hyperæmic and eroded, and the preputial sac contains a creamy-yellowish purulent discharge, having a very offensive odour. In severe cases the erosions may become deep and extensive, and extreme œdema and swelling of the whole prepuce occur.

Treatment.—The preputial sac should be frequently sponged out with an antiseptic lotion, and where there is considerable œdema a prolonged soaking of the penis in hot water is advisable. If the foreskin can be retracted, wash the glans and prepuce with a mild antiseptic lotion, and touch any deep erosions with a 10 per cent solution of nitrate of silver. Dry thoroughly, dust with dusting powder,¹ and finally insert a thin layer of cotton-wool between the glans and the foreskin. The dressing should be removed and the preputial sac washed out every few hours.

When the acute symptoms have passed off, circumcision should be performed. In resistant cases, especially where the foreskin cannot be retracted, it may be necessary to slit up the dorsum of the prepuce, and to complete the circumcision later, after subsidence of the inflammation.

Erosive and Gangrenous Balanitis.—*Etiology.*—Two organisms which always occur together have been described as the causal agents of this disease, viz. a fusiform bacillus or vibrio, and a spirochæte. Corbus (1913) found the same organisms in Vincent's angina. The predisposing factors to an infection by these organisms are a phimotic foreskin and unnatural sexual relations.

The vibrios, according to Corbus, are slightly curved rods, with pointed ends measuring 2μ in length and 0.8μ in width. They are Gram-positive, and grow under anaerobic conditions on serum agar. They are found deep down in the necrotic patches, whereas the spirochæte is found in the superficial regions. The spirochætes are Gram-negative. Scherber does not believe in the pathogenicity of the vibrio or fusiform bacillus. It is

¹ The following dusting powder will be found satisfactory :—

Bismuth. subgall.	.	.	.	grs. 20.
Bismuth. tribromo-phenol	.	.	.	grs. 20.
Zinc. oxid.	.	.	.	ʒi
Magnes. carb. levis.	.	.	.	grs. 20.
Pulv. amyl.	.	.	.	ad ʒi.

non-pathogenic to animals, and he considers that the spirochaetes are responsible for the lesions.

Course.—Erosive and gangrenous balanitis is a specific infectious venereal disease, and has been definitely described as a fourth venereal disease. Corbus clinically divides the disease into two types—(1) Balanitis erosiva circinata; and (2) Balanitis gangrenosa. Scherber and Müller, however, pointed out that the whole question is really one of degree.

The most common sites affected are the sulcus coronarius; next, the inner side of the prepuce; and thirdly, the glans itself. The incubation period is short—forty-eight hours. The disease usually reaches its height of development in four to eight days after exposure to infection. In very rare cases the incubation period may be as long as four weeks.

In the mild erosive type there is a considerable amount of itching, burning sensation behind the prepuce, and purulent discharge with a very foul odour. The affected part shows a flaking of the epithelium with small, shallow, bright red erosions. These are surrounded by a small white zone, which represents the remains of the necrotic epithelium. There are practically no constitutional symptoms, and the condition, according to Bataille and Berdal (1891), may spontaneously recover in four to five days under appropriate treatment. Scherber has seen spontaneous healing almost completed in forty-eight hours by simply washing and exposing the part to the air by retracting the foreskin.

In the severe or gangrenous type there is marked phimosis and œdema of the subcutaneous tissue of the penis, so that the foreskin cannot be retracted. The inguinal glands may be enlarged, and the dorsal lymphatics of the penis may be palpable.

The condition may be accompanied with constitutional symptoms and fever ranging from 100° to 101° F.

Exposure of the glans by retracting the foreskin or, should this not be possible, by making a dorsal slit through the prepuce, will reveal the site of erosion. Small rounded ulcers will be observed inside the area of the erosions. These ulcers vary in size according to the degree of severity of the disease; for example, they may become confluent and extend over a considerable area of the site affected. The bases of the ulcers show a closely adherent false membrane, and there may be a considerable amount of necrosis and gangrene of the foreskin over the ulcers and the surrounding tissues.

Ulcers situated on the glans tend to erode deep into its substance, presenting deep vertical edges, while the surrounding tissue may show gangrene. This is sometimes so severe as to cause complete destruction of the glans, and may even involve a considerable area of the penis.

Treatment.—In the mild cases the foreskin should be retracted, so as to expose the glans to the air. The glans penis is bathed frequently with hydrogen peroxide lotion or some other mild antiseptic lotion.

In the severe cases the glans is exposed by slitting up the dorsum of the prepuce. The part is then frequently washed with hydrogen peroxide lotion and a peroxide dressing applied loosely, so as not to exclude the air too much.

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PART III

PROBLEMS OF IMMUNITY AND THE COMPLEMENT-FIXATION TEST

CHAPTER XXV

THE PROBLEM OF IMMUNITY TO THE GONOCOCCUS

NATURAL INHERITED IMMUNITY—LOCAL IMMUNITY—ANIMAL EXPERIMENTS—INJECTIONS INTO PERITONEUM AND OTHER SEROUS CAVITIES—INTRAVENOUS INJECTION—SUBCUTANEOUS INJECTION—ANTERIOR CHAMBER OF EYE—CONCLUSIONS REGARDING NATURAL IMMUNITY OF ANIMALS—AUTHOR'S EXPERIMENTS

Natural Inherent Immunity.—Man is the most susceptible animal to the gonococcus. Indeed, he is the only susceptible animal, and there is no definite evidence that any human being is born with any true natural immunity to the disease.

Experiments on Man.—(a) Welander (1884) produced a gonorrhœa in man by injecting gonorrhœal pus into the urethra.

(b) Bumm (1885) inoculated a pure culture of the gonococcus into the urethra of a woman, and produced a typical gonorrhœa which lasted for three weeks. The pus from the urethra contained the specific germ.

(c) Bockhart (1886) injected a culture of the gonococcus into the urethra of a general paralytic (in the last stage of the illness). It resulted in a typical gonorrhœa, followed by a suppurative nephritis. The gonococcus was found in the pus of the urethra and in the abscess of the kidney.

(d) Bokai (1880) inoculated pure cultures into the urethræ of six students and produced a gonorrhœa in each case. Brenner, Wertheim (1894), Finger (1894), Schlagenhauser (1894), and Kiefer (1895) also obtained positive results in the same manner. Wertheim found that cultures were infectious even up to the thirtieth generation.

(e) A few instances of natural immunity have been reported by Welander (1896), Epstein, and others. The evidence to the contrary, however, is overwhelming, since practically all experimental inoculations into the urethra have been followed by the disease. Moreover, the enormous accumulations of clinical experience are entirely in favour of the absence of any natural resistance in mankind.

Local Immunity.—Perhaps one might claim that a kind of "local immunity" is responsible for the variation in the susceptibility of different mucous membranes; and variation in age seems also to play some rôle. We know, for example, that the urethral and rectal mucous membrane is susceptible at every age. The vagina and conjunctiva are highly susceptible in childhood, whilst in the case of adults they are seldom affected.

The mucous surface of the bladder is seldom attacked by the gonococcus, and an infection of the mouth is a great rarity.

There can be no doubt that the explanation of the varying susceptibility of different mucous membranes is due largely to histological factors. Pavement epithelium is much more resistant to the gonococcus than cylindrical epithelium. Nevertheless, probably other accessory factors come into play, and Jadassohn (1898) pointed out that the power of resistance could be quickly altered by external conditions; for example, one often gets a gonorrhœal cystitis in the case of retention of urine, and an adult vaginitis will occur where the vaginal epithelium is injured or macerated.

Although most will agree that no true inborn resistance to gonorrhœa occurs in man, yet some are inclined to believe that certain individuals are more susceptible than others. According to Bruck (1912), however, it has been demonstrated that the predisposing factors in by far the greater number of susceptible cases are entirely local, and have no dependence upon a true immunity. Thus it is known that long-continued and repeated coitus, a wide urethral orifice, and a long foreskin predispose more to gonorrhœal infection than the opposite state of affairs. On the other hand, the predisposition of certain individuals to metastatic infections calls for a further explanation. It is often maintained that metastases are caused by a specially virulent strain of the gonococcus. Yet instances have been cited by Jadassohn (1898) where a certain individual always develops a metastatic affection with each different gonorrhœal infection. Further, he quotes the occurrence of metastasis in two brothers infected with different strains. In these cases the individual susceptibility can perhaps be explained satisfactorily through anatomical factors. Finger considers that it is due to the superficial situation of the capillaries in the urethra. Others maintain that it may occur due to damage and breakage of the integrity of the mucous membrane by instruments, such as catheters, etc.

On the other hand, Tommasoli (1900) and Wohl put forward the view that it may be due to some different bio-chemical factor in the constitution.

The subcutaneous tissues of man do not appear to be particularly susceptible to the gonococcus. Wertheim (1892) introduced live cultures of the germ under his own skin. This produced a circumscribed inflammation without any suppuration. Steinschneider (1893) repeated this experiment with negative results.

Experiments with Animals.—All the lower animals, dogs, rabbits, horses, etc., etc., as well as monkeys and the anthropoid apes, have a decided natural inborn immunity to gonorrhœa. Practically all of the numerous experiments by various workers, who have attempted to produce in animals a genuine gonorrhœal infection like that which occurs in man, have up to the present given negative results. Neither by inoculation of the urethral nor of the conjunctival mucous membrane is there produced in animals any multiplication of the gonococci. The germ is non-infectious to animals, because it is practically incapable of multiplying or extending into the tissues when inoculated or injected. It is able, however, to exert a definite toxic influence according to the dose injected, and when living gonococci are introduced subcutaneously or intra-peritoneally into an animal the germ may multiply locally for a very short time, but they rapidly die and autolyse, and the symptoms produced are entirely due to the liberated toxins. A sufficiently large dose of the germ or its toxin is capable of killing the animal. Bruck (1912) failed completely in his attempts to produce gonorrhœa in anthropoid apes by intra-urethral inoculations of the germs, and he states that no one has ever succeeded in producing at any time an evident gonorrhœa, identical or analogous with that of man, on the mucous membrane of any animal. Jos. Koch and Sieskind (1912) inoculated the different mucous membranes of young rabbits, dogs, and monkeys with large quantities of gonorrhœal pus, but failed to produce any active disease, just as happened in the experiments of earlier workers. Heller (1896) claims that he produced a gonorrhœal ophthalmia of five weeks' duration in young rabbits by inoculation of infective pus. Legrain (1891) produced in guinea-pigs a mild purulent conjunctivitis with gonococci in the interior

of the leucocytes. Morax (1894) maintains that conjunctivitis produced in young rabbits by inoculation with the gonococcus is simply an inflammation caused by the toxin, and that dead cultures produce the same effect. Hewes claims an artificially produced genital gonorrhœa in a bitch. Colombini (1898) maintains that he successfully inoculated the genital mucous membrane of dogs and rabbits, and Fonseca reports that he also produced a slight gonorrhœa in a rabbit.

Against these successful inoculation experiments, however, the literature shows a far greater number of negative results.

Neisser (1882), Leistikow (1882), Krause (1882), Bumm (1885), Steinschneider (1893), Finger, Ghon, and Schlagenhauser (1894), Nicolaysen (1897), De Christmas (1897 and 1900), Schäffer (1896), Raymond, Heiman (1895 and 1896), Grosz and Kraus (1898), Charrier, Scholtz (1899), Morax (1894), and Deyke (1896), etc., failed entirely to produce gonorrhœa of the mucous membranes of animals. Jadassohn (1898) attempted in vain to produce a gonorrhœal ophthalmia in the conjunctiva of young rats.

Besse and Christidès (1919) state that a predisposition has to be induced before guinea-pigs can be used for experimental research with the gonococcus. They think that this could be accomplished by modifying the diet, but the three animals tested did not yield conclusive results.

Peritoneum.—With regard to the artificial infection of the serous membranes of animals, more success seems to have been obtained. The experiments of Wertheim claim a special importance, because they first showed that the gonococcus may be infectious to animals under certain conditions. He introduced, for example, a serum-agar culture of the germ into the abdominal cavity of white mice and produced in these animals an acute peritonitis. In the sero-purulent exudate on the peritoneum, virulent gonococci were found even up to the fifth day. Guinea-pigs were less susceptible, and still less rabbits and rats. Dogs were scarcely susceptible at all.

Maslofsky (1899), Moskalew (1905), Veillon and Halle (1896) also produced in white mice, by intra-peritoneal injection of live cultures, a circumscribed peritonitis with local multiplication of the gonococci.

Maslofsky, by inoculating gonococci into the uterus of a rabbit, produced a suppuration of the Fallopian tubes with fatal peritonitis in twenty-four hours.

According to Morax (1894) the inoculation of very virulent cultures into the peritoneum of young rabbits can cause death by septicæmia.

Nicolaysen (1897) injected serum-agar cultures of gonococci emulsified in sterile water into the peritoneal cavity of mice and guinea-pigs, with the result that two-thirds of the animals died within twenty-four hours. Post-mortem examination showed very little beyond a trifling amount of clear peritoneal exudate. Smear preparations of this exudate showed a few round cells and varying numbers of gonococci, partly free and partly intracellular. He was able to obtain pure cultures of the germ from the peritoneal exudate of the mice. Exceptionally a sparse culture was obtained from the heart blood, but never from the spleen. Similarly with the guinea-pigs, pure cultures could be obtained from the peritoneum immediately after death, and exceptionally he succeeded also in cultivating the germ from the heart blood.

In these experiments Nicolaysen was led to believe that the gonococci injected had not multiplied in numbers. He was unable to observe any increase of virulence by repeated passage through animals.

An investigation by Wildbolz (1902) showed that the gonococci may increase in number and produce a general infection. He injected a thirty-five-days-old serum-bouillon culture, in which only very occasional involution forms of gonococci were present, into the peritoneal cavity of a guinea-pig, with the result that large numbers of gonococci appeared in the heart blood of this animal. Jundell (1900), Morax (1894), and Scholtz (1899) were also able to demonstrate the presence of the germ in the heart blood of intra-peritoneally injected animals. The latter author maintained that a slight increase in the

number of gonococci, and even a spread to other organs, could only be recognised in heavily inoculated animals. This slight increase, he considered, took place probably at the time of the death agony, or after the death of the animal, and he believed that the penetration to distant organs was only brought about passively by the agency of the leucocytes. He was only able to obtain live germs up to about twenty hours after the death of the animal. Wildbolz (1902) believed that after intra-peritoneal injection a true, but transient, multiplication occurred. After two to three days, however, the peritoneal cavity was again free of the germs.

Wertheim was able to follow the penetration of the gonococci from the peritoneum into the muscular system. Generally, however, they remained local.

Pinto (1904) inoculated large doses of cultures into the peritoneum of very young rabbits, and obtained a septicæmia. At the end of a series of passages through various rabbits, the virulence of the gonococcus was raised to such a point that a dose of 0.00002 gram per kilogram weight of rabbit was fatal.

His researches have been confirmed by Bruckner and Christéanu (1906), who were able to raise the virulence of the germ to a very considerable degree by a series of passages in the peritoneum of the rabbit and the cat.

Martha Wollstein (1907) found that half of the emulsion of live gonococci, from a pint Blake bottle of serum-agar culture twenty-four hours old, always killed a guinea-pig of 170 to 200 grams weight in twenty to twenty-four hours when injected intra-peritoneally. For mice an emulsion from one serum-agar slant was lethal, but half this amount was sublethal. The virulence of the germs decreased rapidly during subculture. A recently isolated culture of the second or third generation was always lethal, but after the seventeenth or eighteenth generation the entire culture of a Blake bottle failed to cause death in guinea-pigs. Post-mortems in fatal cases showed œdema of the pancreas and the surrounding tissues, with a layer of pus or fibrin over the liver, spleen, or omentum. There also occurred congestion and hæmorrhage in the adrenal glands, as well as small hæmorrhages into the peritoneum and mesentery. She states that multiplication of the cocci was more in evidence after inoculation with both culture and extract than when a culture was injected alone. The presence of extract or toxin, which was obtained by autolysing the gonococci, seemed to inhibit phagocytosis.

Torrey (1908) states that an emulsion of live cocci made from three-fourths of a square inch of culture from a recently isolated toxic strain was nearly lethal to a guinea-pig weighing 200 grams, and that one and a half square inches of such a culture was always lethal.

After subculturing a virulent strain for a year, the virulence decreased, since after that time it took one and a half to three square inches of culture to kill, and later still it required four square inches. He found that a fatal dose caused a fall in the temperature as well as convulsions and paresis of the hind limbs. Flexner (1907) noticed similar effects in guinea-pigs after a fatal dose of meningococci. On post-mortem examination the peritoneal cavity was found to be full of yellow fluid, clear or slightly bloody, with deposits of pus on the liver and abdominal walls. The suprarenal capsules were enlarged and intensely hyperæmic (this was also observed by Vannod). Death always occurred in less than thirty-six hours. Twenty hours after the intra-peritoneal injection of a lethal dose, he was able to get cultures of the germ from the blood just prior to the death of the animal. Where, however, the dose was sublethal, the heart blood was found to be sterile ten hours after the injection. After the injection there was a leucopenia which lasted for about seven hours.

Injections into other Serous Cavities. Jundell (1900) produced a cheesy-like exudate by injecting gonococci into the pleural and pericardial cavities of rabbits and guinea-pigs. He was unable, however, to find any trace of the germ in these exudates. Pizzini caused in rabbits a pleurisy of a sero-fibrinous character, which caused the death of the animals in about three days after the intra-pleural injection.

Similar results were obtained by F. Meyer (1903) with injections into the endocardium, and by van Steenberghe and Grysez (1906) with regard to the meninges.

Finger, Ghon, and Schlagenhafer (1894), and Nicolaysen (1897) succeeded in producing acute transient inflammation in the joints of guinea-pigs, rabbits, and dogs by intrasynovial injection of cultures. Gonococci, however, could not be detected afterwards in the joint exudates. Sorrentino claims to have produced in this way a true gonorrhoeal joint inflammation in dogs and rabbits.

Intravenous Injection.—Pompéani (1898) was able to find the gonococci in the blood of animals up to about forty-eight hours after intravenous injections of live emulsions.

Subcutaneous Injection.—According to Reale, Jundell (1900), and Jos. Koch (1912), injections of live gonococci into the connective tissues produced no inflammation. Steinschneider and Schäffer (1895) implanted silk threads impregnated with live gonococci into the subcutaneous tissues of animals without results. Maslofsky (1899), however, found that sterile abscesses sometimes were produced as the result of subcutaneous injection, and Finger also obtained a small abscess on one occasion.

Anterior Chamber of the Eye.—Bruck (1912) and Meirowsky injected living gonococci into the anterior chamber of the eye in rabbits, and produced thereby a suppuration or hypopyon. This pus, however, became sterile and free from gonococci in about three days.

Mezinescu, D., and Holban, D. (1919), inoculated cultures of gonococci into the eyes of rabbits. They were unable to confirm the results of Debré and Paraf, who claimed that they were able to produce an infection by injecting gonococci into the anterior chamber of the eye. They suggest that the results of Debré and Paraf represent merely a toxic effect. Injection of virulent cultures of gonococci into the anterior chamber may be followed by suppuration, with perforation of the cornea, but it is not possible to demonstrate the cocci in the pus, nor can the condition be set up in another rabbit by inoculation with the pus. A similar condition can be produced by inoculating an emulsion of cocci which have been killed by heat, and, as a matter of fact, living gonococci disappear within a few hours when kept in contact with the fluid from the anterior chamber of a rabbit's eye.

Conclusions regarding the Natural Immunity of Animals.—It must be concluded that, in spite of numerous experiments and a most varied technique, no certain or definite gonococcal infection has hitherto been transmitted to any of the lower animals. Although animals exhibit a very strong natural immunity towards the germ, it must not be imagined that it will always be quite impossible to cause in them a true gonococcal infection. This may only be a question of time and technique. It should be remembered that for over a hundred years it was considered quite impossible to infect animals with syphilis, but in recent years successful infections have been established in rabbits.

So far we are unable to define the nature of the natural immunity of the mucous membrane of animals to gonorrhoea. It can hardly be ascribed to purely anatomical causes. For some time it was believed that the natural high temperature of animals might account for their resistance, but it was found by experiment that even when the temperature was artificially reduced no further success was obtained by inoculation. It seems more likely that the natural immunity of the lower animals is due to bio-chemical causes. The gonococcus in culture experiments always grows best on media which contains some human albumin, such as blood serum, ascitic fluid, etc. On the other hand, when the albumins, such as the serum of certain animals, are employed, very often the growths are extremely poor and may be entirely inhibited.

Torrey (1908) states that certain strains of gonococci are very sensitive to the bactericidal action of fresh normal rabbit serum, while other strains are decidedly more resistant. In testing the bactericidal effect of the sera he used the method recommended by Neisser and Wechsberg (1901). A few drops of meat bouillon are added to each tube containing the dilutions of the serum to be tested. These, as well as the controls, are sown with a

definite amount of the germ, incubated for a certain time, and then plated. Bactericidal properties are estimated from the scarcity or absence of colonies on the culture plates.

Martin (1910)¹ studied very carefully the effect of rabbit and other sera upon the meningococcus and the gonococcus. He states that the technique is difficult, and many fallacies are apt to arise, because the saline emulsions of gonococci are liable to die rapidly, and also because the serum of normal rabbits varies from day to day.

As a result of his experiments he came to the following conclusions :—

(1) The normal serum of the guinea-pig, rabbit, cat, and man may be bactericidal towards gonococci and meningococci. Cat serum showed the most marked effect on both these organisms.

(2) A normal serum, *e.g.* guinea-pig or human serum, may be distinctly bactericidal to the meningococcus and yet have practically no effect on the gonococcus.

(3) The serum of a normal rabbit may vary in its bactericidal properties within short periods of time, more especially with regard to the meningococcus.

(4) The bactericidal property of the serum could be removed by heating it to about 60° C. Thus a cat's serum very strongly bactericidal to the gonococcus became quite innocuous after heating.

The Author's Experiments.—In 1917 the author carried out several experiments with rabbit serum and plasma, and although unacquainted with the literature on the subject, came to almost the same conclusions as enumerated by Martin.

Experiment I.—One cubic centimetre of citrated rabbit plasma, citrated human plasma, rabbit serum, human serum, and normal saline was placed respectively in five different tubes. To each was added five drops of a fresh gonococcal emulsion in saline. The tubes were shaken and then placed in the incubator at 37° C. for two hours. Five culture slants were inoculated respectively with three drops of the mixture from each tube, and incubated at 37° C.

Result after eighteen hours' incubation :—

Culture from rabbit plasma—no growth.

Culture from rabbit serum—no growth.

Culture from human plasma—marked growth of gonococci.

Culture from human serum—marked growth of gonococci.

Culture from saline control—marked growth of gonococci.

The two hours' contact with the rabbit plasma and serum, however, did not quite kill the gonococci, since colonies began to develop in the culture tubes after the third day of incubation.

Experiment II.—Rabbit serum 1 c.c. and human serum 1 c.c. were heated to 60° C. for fifteen minutes to destroy the complement. Five drops of fresh gonococcal emulsion in saline were added to each. After seventeen hours' incubation at 37° C., three drops from each tube and from the saline control were inoculated on to slope cultures.

Result after eighteen hours' incubation :—

Culture from rabbit serum—good growth of gonococci.

Culture from human serum—good growth of gonococci.

Culture from saline control—good growth of gonococci.

It would therefore appear that the bactericidal power of the rabbit's serum is rendered inactive by the destruction of the complement.

Experiment III.—To 0.75 c.c. of inactivated rabbit serum (heated to 60° C. for fifteen minutes) was added 0.25 c.c. of fresh human serum, and also five drops of fresh gonococcal emulsion in saline. The tube was incubated overnight along with a control tube. Next morning three drops from each were inoculated on to slope cultures.

Result :—

Good growth from the control, but no growth from the rabbit serum which had been activated with the fresh human serum.

¹ Martin states that the first account of the bactericidal action of serum on the meningococcus was published by Davis in 1907. Martin studied it independently in 1907, and an account of this work was published by Martin and Ivy McKenzie (1908).

The bactericidal agent in the rabbit's serum is evidently not destroyed by heat at 60° C. for fifteen minutes, but it is only able to exert its action in the presence of complement.

Experiment IV.—Fresh rabbit serum was placed in the ice chest over night. Next day five drops of fresh gonococcal emulsion were added to 1 c.c. of the pure serum, which was then incubated at 37° C. From this, culture tubes were inoculated after fifteen minutes, thirty minutes, sixty minutes, and ninety minutes' incubation respectively. No growth occurred in any of the tubes.

Also five drops of gonococcal emulsion were added to each of four dilutions of the rabbit serum, viz. 1 in 5, 1 in 10, 1 in 20, and 1 in 50. After two hours' incubation culture tubes were inoculated, and again no growth appeared in any of the tubes.

Experiment V.—The details need not be given, but it showed that the sera from different rabbits vary in potency, some being more bactericidal to the gonococcus than others.

Experiment VI.—Rabbit's sera of known bactericidal power were incubated with equal parts of gonococcal emulsion for two hours, then centrifuged and the supernatant fluid drawn off. The supernatant fluids were again inoculated with fresh gonococci. This time, however, the bactericidal effect was not so marked. This experiment was not a very successful one; nevertheless it showed evidence that the first addition of gonococci removed a certain amount of the bactericidal property from the sera.

Experiment VII.—The sera of four different rabbits, A, B, C, and D, were each mixed with an equal amount of fresh gonococcal emulsion in saline, and then incubated for three hours at 37° C.

Result: A showed marked agglutination of the gonococci.

B and C showed some agglutination, but not so marked.

D showed very little or no agglutination.

After the agglutination in A was complete the supernatant fluid was pipetted off, again mixed with gonococci, and incubated. The result showed a considerable diminution in agglutinating power, indicating that part of the agglutinins had been used up with the first admixture with gonococci.

Experiment VIII.—This was a repetition of Experiment VII., except that the sera was first heated to 60° C. for fifteen minutes, with the result that no agglutination whatsoever occurred.

Experiment IX.—It was ascertained that a gonococcal emulsion in saline died as a rule after about twenty hours' incubation at 37° C. The addition of human serum to the saline emulsion prolonged the life of the germ.

Experiment X.—Tubes of glucose-plasma agar medium were made up as described in Chapter VI., with the exception that rabbit plasma instead of human plasma was used. (It was first ascertained that the plasma of this rabbit was bactericidal to the gonococcus.) Special care was taken not to heat the plasma, by cooling the agar to about 40° C. before adding the former. Contrary to expectation, the gonococcus grew very profusely on this medium. Perhaps the bactericidal properties of the rabbit plasma had been rendered impotent by adsorption of the complement into the agar.

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CHAPTER XXVI

ACQUIRED IMMUNITY

NATURAL—ARTIFICIAL—AGGLUTININS—PRECIPITINS—OPSONINS—
BACTERIOLYSINS—AGGRESSINS

Naturally Acquired Immunity.—The problem of acquired immunity towards the gonococcus still needs much investigation. Carl Bruck (1912) maintains that it has been proved by numerous experiments (Finger, Ghon, and Schlagenhauser (1894)), as well as by clinical experience, that—

- (1) An attack of gonorrhœa never protects against a new infection.
- (2) A mucous membrane attack of gonorrhœa never protects against a metastasis.
- (3) A continuing (chronic) gonorrhœa does not protect against a superinfection.

In other words, there is no real acquired immunity (not even temporary) either during or after the disease.

Nevertheless, he states that there are two clinical phenomena which point to the existence of some condition akin to immunity, and which must not be overlooked.

First, it is a well-known fact that the occurrence of an epididymitis is followed by a retrogression or temporary disappearance of the primary urethral gonorrhœa. Some have supposed that the explanation must be due to the fever which often accompanies an acute epididymitis; yet the same phenomenon is also observed in cases with no fever. Jadassohn considers that the phenomenon is probably due to the development of anti-gonococcal substances. In acute epididymitis the toxins produced by the gonococcus are absorbed in greater quantity than in the case of urethral gonorrhœa, and hence in the former condition there is a much greater stimulus to the production of immune bodies. In harmony with this view is the definite existence of complement-deviating substances in the blood of epididymitis cases, as first demonstrated by Bruck (1906).

The author has found, through the complement-fixation test (see Chapter XXIX.), that the amount of anti-gonococcal substance developed in the blood during an attack of acute epididymitis is at least double or treble the amount developed in those cases where the urethra alone is involved.

The second clinical phenomenon which seems to point to the development of immunity is the fact that an acute gonorrhœa will gradually and spontaneously dwindle away without any treatment. Thus an acute urethral discharge will eventually become subacute and then chronic, and may even disappear without any medical interference.

This spontaneous retrogression of acute gonorrhœa was formerly explained as due partly to a gradual reduction in the virulence of the germ, and partly to a development of tolerance on the part of the mucous membrane. These were, of course, expressions which conveyed no precise idea regarding the chemical and physiological happenings. Jadassohn considered that the changes which occurred in the mucous membrane (metaplasia of the cylindrical epithelium into embryonic pavement epithelium) were not quite sufficient to explain the retrogression of the disease, since on the one hand pavement epithelium can be attacked by the gonococcus, and on the other hand cylindrical epithelium

can be resistant to it. He was more inclined to believe, along with Pizzini, that the dwindling of an acute attack and the reduced severity of many repeated infections were due to some unknown bio-chemical changes in the mucous membrane.

Immunity in chronic gonorrhœa was first studied by Finger, Ghon, and Schlagenhauer (1894). These observers injected equal quantities of a pure gonococcal culture into the urethras of four chronic gonorrhœal subjects (two showed gonococci in the urethral discharge; two were apparently free). The result of the injection in all four cases was a typical acute gonorrhœa with numerous gonococci, after forty-eight hours.

Wertheim cultivated the gonococcus from a case of chronic gonorrhœa, and reinoculated the patient seven times per urethram with his own germs, without any aggravation of the chronic symptoms. The same culture, however, when injected into a normal urethra produced an acute gonorrhœa. A pure culture was obtained from this latter case, and again injected into the previous chronic case, with the result that an acute exacerbation of the disease was produced. Wertheim concluded that the urethral mucous membrane in the course of gonorrhœa becomes immune towards its own homologous strain of gonococcus. If, however, this homologous strain has its virulence increased by a single passage through a normal mucous membrane, it will again become pathogenic for the chronically affected urethra, so that it acts like a new heterologous strain.

Contrary to this view, Jadassohn has shown that although certain cases of chronic gonorrhœa can be acutely reinfected by their own germ after passage through another, yet other cases occur in which a superinfection cannot be produced either with homologous or heterologous strains.

Thus Wertheim assumed that a chronically affected urethra only produced a partial immunity towards its own strain of germ, whilst Jadassohn believed that a certain amount of true immunity eventually developed, which was perhaps analogous with the condition which arose in syphilitics wherein a second primary infection could not be induced.

A partial acquired immunity of the mucous membrane in chronic gonorrhœa has been noted clinically by Neisser, Finger, Jadassohn, Scholtz, and others, more especially in the case of gonorrhœal subjects.

Finger states that a man with an old urethritis still harbouring gonococci is immune to the extent that no more acute exacerbations occur. When he marries, however, these gonococci are virulent to his wife, and produce a gonorrhœa in her. Through transmission, as it were, on to a new soil, these gonococci now acquire a new virulence for the man, and he is again reinfected from his wife. Soon, however, both become partially immune and cease to become infectious to each other. If, however, a third person comes along, say a second husband or wife, that person will also acquire the disease in an acute form, from the one or the other.

Jadassohn, however, believes that the immunity developed in many cases of chronic gonorrhœa is sufficiently strong to prevent a superinfection with a homologous strain, even though it be passed through a new individual. Thus it is usually accepted that if a man with chronic gonorrhœa infects his wife, he does not necessarily always reacquire an acute attack from her.

Although the existence of some acquired immunity in the mucous membrane must be admitted, yet there is sufficient clinical evidence to show that this resistance may only last for a short time. Complete susceptibility of the mucosa may very quickly follow a transient immunity. Thus when the urethral discharge has been latent for some time, it is quite possible to get an acute discharge resembling a fresh attack due to auto-inoculation with some latent gonococci set free from the urethral glands or from the prostate.

Although we are now able to demonstrate the presence of anti-gonococcal substances in the blood of gonorrhœal subjects, we are still ignorant as to their bio-chemistry and the physiological processes which lead to their production. We are also ignorant with regard to the local bio-chemical changes which take place in the mucosal cells. We can only

follow Ehrlich's view by assuming that there is some alteration in their "receptors." At any rate, as already mentioned, the local immunity which develops is not merely due to a change of epithelium from the cylindrical to the pavement type. The histological investigations of Bumm, Jadassohn, and P. Cohn (1908) show that there may be found in chronic gonorrhœa areas of metaplasied flat epithelial cells infected with numerous gonococci, whilst the normal cylindrical epithelium surrounding these areas may remain continually free from infection.

In some manner, therefore, the true cylindrical epithelial cells appear to develop a resistance towards the germ, and it is quite possible that Jadassohn was correct in considering that this immunity process was rather held in check than encouraged by employing too energetic local treatment.

It would appear that the following conclusions may be drawn from the above evidence and arguments:—

(1) A partial immunity is developed in gonorrhœa, more particularly towards the given infecting (homologous) strain.

(2) This immunity is general, as the anti-gonococcal substances can be detected in the blood.

(3) There is also a local immunity with regard to the mucous membrane itself. This local immunity may simply be a manifestation of the general circulating anti-substances, or it may be due partly to bio-chemical changes in the cylindrical epithelial cells themselves, and partly to a histological change from the latter to the more resistant flat epithelial type.

Artificial acquired Immunity to the Gonococcus and its Toxins.—The earliest experiments to induce the formation of anti-gonococcal substances aimed at the production of anti-toxins against the poison of the germ.

Wassermann (1897-1898), Wertheim (1894), Mendez and Calvino (1908), and others attempted to produce an anti-toxic serum in man and animals, but their efforts were entirely unsuccessful. De Christmas alone claims success in this respect. For immunisation he used old cultures in a fluid medium. He states that most toxin was produced in a peptone-free medium composed of 75 per cent ascitic fluid and 25 per cent of bouillon (see Chapter XI.). The toxic fluid was filtered through paper or talc and then injected into animals. The efficacy of the poison was established by intra-cerebral injections into young guinea-pigs. The minimum lethal dose for guinea-pigs of 250 to 300 grammes weight was, as a rule, 1/250 to 1/500 c.c. of the filtered fluid. These minute doses of the toxic fluid were mixed with 0.05 c.c. of normal saline, and injected about two to three millimetres deep into the brain substance of one hemisphere. Usually the guinea-pigs remained quite lively for four to five hours, then signs of paralysis and spasmodic convulsions set in. They died, as a rule, within twelve to twenty-four hours.

He claims to have immunised goats against the poison by subcutaneous injections of large quantities of the toxic fluid, in gradually increasing doses.

After a month's treatment, the serum of the goats showed a marked anti-toxic power. When such serum was mixed with the toxin the latter was rendered inactive and innocuous to guinea-pigs. He found that 0.5 c.c. of the anti-serum could neutralise 10 c.c. or 5000 times the lethal dose of toxin to guinea-pigs, provided they were mixed together before injection into the animals.

The neutralisation was not accomplished immediately on mixing. It required three to four hours at 15° C. When injected separately it required much more of the anti-serum to neutralise the poison.

Thus when toxin was injected into one hemisphere of the brain and anti-serum into the other, simultaneously, it required 0.05 c.c. of the latter to neutralise a double lethal dose of the former. Thus 0.05 c.c. of the anti-serum was able to save the life of a guinea-pig against twice the lethal dose of the toxin. When the serum was injected intravenously twenty hours before the toxin was administered, it was found that 1 c.c. of the former

protected the animal against 0.01 c.c. of the latter. Subcutaneous, intravenous or intra-peritoneal injections of a large dose of 1 to 5 c.c. protected against the toxin when the latter was injected forty-eight hours later. He was never able, however, to cure animals already showing symptoms, even with large injections of anti-serum. The animals were only saved when the latter was injected before the administration of the toxin. Further, the immunity produced in the animal by an injection of anti-serum was very transitory, disappearing as a rule forty-eight hours after the injection, though in some cases it protected the animal against intra-cerebral injections for three days.

De Christmas also claims that an active immunity was developed in guinea-pigs against gono-toxin, when the latter was injected into the brain. He found it very difficult to gauge the dose, such that it was sublethal yet sufficiently strong to stimulate the formation of anti-toxin. Nevertheless in those cases in which he managed to gauge the dose, he succeeded in proving that a strong immunity of the whole brain had been produced. Smaller doses which were not sufficient to cause death conferred on the animal a strong immunity which allowed it to resist new intra-cerebral inoculations, and also large doses of the toxin injected under the skin on several occasions caused immunity against intra-cerebral inoculation.

Vannod (1906-1907) made a further research on the subject, and found that cultures of gonococci in the bouillon of de Christmas developed their maximum toxicity towards rabbits after about twenty days' incubation. The amount of toxin produced in different cultures, however, was very irregular. He was able to obtain from the gonococcus a nucleo-protein which was fatal to rabbits; and further, he ascertained that rabbits treated with this substance developed in their serum a definite though feeble anti-toxic effect.

Funck (1907) injected a gono-toxin, obtained from inspissated ascitic bouillon cultures, into horses, and claims to have developed anti-toxic properties in their sera.

According to Torrey (1908) the gonococcal toxin is an endo-toxin, and different strains of the germ vary greatly in their poisonous properties. He was unable to confirm the experiments of de Christmas, since he failed to produce immunity to the poison in guinea-pigs. On the contrary, he found that these animals tended rather to develop an increased sensitiveness by repeated injections. He states that he is in agreement with Wassermann (1898), Jundell (1900), and Vannod (1907), who found that no immunity other than a slight tolerance and resistance to gono-toxin could be induced in small laboratory animals, and that anti-toxin production was impossible.

Torrey inoculated guinea-pigs with sublethal doses of the toxin at intervals of a week or more. Although after the third or fourth injection there might be some indication of slight tolerance, on further treatments this frequently gave way to a sudden hypersensitiveness. Other pigs became marasmic and succumbed after progressive emaciation, as has been described by Wassermann (1898), Jundell (1900), and Moltschanoff (1899). Occasionally partial paralysis preceded death, appearing first in the hind limbs and then in the fore limbs. Moltschanoff has shown that this paresis is accompanied by degenerative changes in the nerve cells of the anterior horns of the spinal cord. In a number of instances Torrey noticed phenomena suggestive of anaphylaxis, since the first injection of toxin seemed to sensitise the animals in such a way that they were much more distressed by a second injection of the same dose given fifteen to twenty-three days later.

Wells (1918) states that so far no successful anti-toxic serum has ever been produced towards an endo-toxin. Success in this respect has only been attained so far with exo-toxins.

Although there appears to be considerable doubt as to the possibility of developing immune bodies against the toxin of the gonococcus, nevertheless the majority of experimenters have demonstrated that a definite immunity can be produced against the gonococcus itself. This immunity is conferred by agglutinins, precipitins, and bacteriolysins. According to Torrey the toxin is derived solely from the bodies of dead or disintegrated

gonococci, and so he claims that it is an endo-toxin. Whether the toxin is exo- or endo- in nature, the writer believes that it is a definite substance, and not identical with the actual protoplasm of the disintegrated germs (see Chapter XXXI. on detoxicated vaccine).

This may help to explain the apparent discrepancies, and it is just possible that de Christmas was not dealing with pure toxin, but with a mixture of toxin and the higher proteins of the disintegrated germs. Torrey, on the other hand, may have filtered his fluid cultures more carefully, and, by getting rid of the disintegrated bodies, was perhaps dealing more with the toxin alone. This subject, however, requires further elucidation. The author has found that the pure toxin completely separated from the gonococcal protoplasm will pass through an animal membrane. It is therefore not a true colloid, and it does not appear to be capable of inducing the formation of anti-substances when injected into animals.

Acquired Immunity to the Gonococcus itself.—As already stated, the great majority of researchers have shown that immune bodies can be developed in man and in animals to the gonococcus itself. These anti-bodies consist of agglutinins, precipitins, bacteriolysins, and complement-deviating substances.

There are quite a series of important works on the specific agglutinins, precipitins, and complement-deviating substances in the serum of animals which have been inoculated with gonococci, and in the serum of patients suffering from the disease.

(a) **Agglutinins.**—The appearance of agglutinins in the blood serum of human beings suffering from gonorrhœa was first observed by Wildbolz (1902) and Baermann (1903) in cases of epididymitis. According to Wildbolz the normal serum of man or of the guinea-pig possesses no agglutinating property. He found, however, that in a patient with gonorrhœal prostatitis the serum agglutinated an old culture of the gonococcus, but not a young culture.

Scholtz (1899), Jundell (1900), and Bruck (1906), on the contrary, were unable to demonstrate such bodies in patients, and Bruck states that at all events agglutination has no importance as a means of diagnosing the disease. The agglutination test has recently been found to be very valuable in the diagnosis of cerebro-spinal meningitis, and by this means the meningococcus has been classified into several types. With regard to gonorrhœa, however, this method has not yet been so thoroughly developed.

In animals, however, which have been inoculated with gonococci, most observers were able to demonstrate the presence of very definite agglutinins in the serum. Thus Wildbolz (1902) produced in guinea-pigs, Bruck (1906) and Warren (1921) in rabbits, and Bruckner and Christéanu (1906) in horses, agglutinins which acted up to a dilution of 1 in 750 by the macroscopic method and to 1 in 2000 microscopically. These agglutinins caused clumping with the meningococcus as well as with the gonococcus. The serum, moreover, possessed a curative power against intra-peritoneal inoculations of gonococci in rabbits. Vannod (1906) found that agglutinins to the gonococcus were developed in the serum of rabbits which he injected with the nucleo-protein which he had derived from the germs. Agglutination was caused by the serum in dilutions of 1 in 200 to 1 in 400. The close relationship between gonococci and meningococci was studied further by Zupnik (1906) and Ruppel (1906). It was shown that moderately strong agglutinating and anti-gonococcal sera which had no action on staphylococci and streptococci, had nevertheless some agglutinating power against the meningococcus; *vice versa* an anti-meningococcal serum also agglutinated the gonococcus. These observers considered therefore that the agglutination test was of doubtful value in the differential diagnosis between the two organisms.

Vannod (1906), Torrey (1907), and Elsler and Huntoon (1909), who studied the question in great detail, considered that the agglutination test served to differentiate the *M. catarrhalis*, the gonococcus, and the meningococcus group from one another, provided that strongly active sera were used and that the results were properly controlled. They pointed out that some strains were difficult to agglutinate, and on the other hand it was

found that the gonococcus was often agglutinated by normal rabbit serum, and that it was rather susceptible to group agglutinins.

Torrey (1907 and 1908) considered that agglutinins for the gonococcus and meningococcus were common to both only when very low dilutions were used.

He found that certain strains of gonococci when injected separately into rabbits produced agglutinins which could be differentiated from each other. Thus he states that strains of gonococci A, B, and C belonging to Type I. produced agglutinins which showed a common reaction, but, on the other hand, strains G, H, and I belonging to Type II. produced agglutinins which would not react with the germs belonging to Type I. No difference could be seen culturally or morphologically between the two types. He concluded that with regard to the manufacture of anti-gonococcal serum it was advisable to inject the animals with many strains of the germ so as to produce a polyvalent anti-serum.

Rogers and Torrey (1907) by immunising sheep with intra-peritoneal injections of culture emulsions heated to 65° C. for half an hour, and later with living cultures, obtained an agglutinating serum which, according to them, possessed curative properties against gonorrhœal rheumatism and gonorrhœa of the urinary passages.

Wollstein (1907) found that the serum of the normal rabbit usually agglutinated the meningococcus and the gonococcus in dilutions of 1 in 10 to 1 in 20. When inoculated some ten times with the live germs the agglutinating power was manifested even in dilutions of 1 in 50 to 1 in 400. There was no very definite specificity noticeable, however, with regard to the two germs.

Dopter and Koch (1908) claim that by the use of the method of absorption of agglutinins a specific agglutination reaction can be demonstrated, even when a given serum agglutinates both the meningococcus and the gonococcus equally before absorption.

Arkwright (1909 and 1912), however, states that since a meningococcal serum may agglutinate some strains of gonococcus, but may affect only a limited number of strains of meningococcus, the method of absorption can only have a very restricted application. Moreover, he maintains that absorption experiments with different strains of meningococcus and a meningococcal serum gave a differentiation between the strains of the meningococcus used, similar to that obtained by Dopfer and Koch between the meningococcus and the gonococcus. Torrey (1907) obtained similar results of the same kind in his studies on the agglutination of the gonococcus. Arkwright (1912) sums up the question by stating that "Meningococci and gonococci appear to fall, as regards agglutination, into sub-groups, the members of which react among themselves, but not with the members of other sub-groups of the same organism; *vide* Torrey (1907) and Arkwright (1909). Unless therefore the serum used was obtained by injecting all the sub-groups, it might fail to produce the reaction with the cocci which were members of the remaining sub-groups, and which had not been injected. A polyvalent serum might give a very uniform reaction with six strains, but not with a seventh or eighth. On the other hand, although a polyvalent meningococcal serum gives a reaction with some strains of gonococcus as well as with some strains of meningococcus, it is possible that a monovalent meningococcal serum might be obtained which had no affinities with any strain of gonococcus. If such a monovalent meningococcal serum gave uniformly positive results with all strains of meningococcus and negative results with all the strains of gonococcus which were available, the result might be significant, and the use of such a serum for the classification of new strains might be of value. Unless, however, a serum with such strictly specific activity can be obtained, serological tests are not of much value for making a final and conclusive diagnosis of a given strain of a meningococcus-like organism."

Arkwright, in the same paper, further concludes that "No satisfactory distinction between meningococci and gonococci can be demonstrated by means of the complement-fixation tests." The writer's researches agree with this conclusion. On the other hand, the more modern researches by Gordon, Hine, Bell and others in connection with the

meningococcus seem to show that agglutination is a reliable means of dividing the various strains into four different groups.

Early in 1918 the author sent Major Bell eleven marked culture tubes, comprising the four different types of meningococci and seven strains of the gonococcus. He was asked to diagnose the type of organism in these cultures by means of the agglutination test and to return his results to the author for confirmation. His diagnosis was correct in ten out of the eleven cultures. It would appear therefore that in the future the agglutination test may yet serve as a reliable means of differentiating between different types of meningococci and gonococci.

Shera (1918) states that Torrey by injecting rabbits with gonococci obtained a homologous serum which agglutinated the germ, even when diluted up to 1 in 700,000, but a heterologous serum only agglutinated up to 1 in 50. This would appear to show that in gonorrhœa, autogenous vaccines are likely to be much more effective therapeutically than stock vaccines.

Nicollé, Jouan, and Debains (1919) studied the differentiation of the gonococcus and the meningococcus by agglutination. They found that when the two antigens were brought into contact with their homologous sera the agglutination is specific. When, however, the antigen is treated in the manner described by Porges as modified by these authors (extraction with HCl and subsequent neutralisation with normal NaOH), a marked difference is obtained, for it is now found that the meningococcus is no longer sensitive to its homologous serum, whereas the gonococcal antigen is unaltered. The authors maintain that the complement-fixation test is unsuitable for differentiating the gonococcus from the meningococcus.

Hermanies (1921) found that gonococci could be differentiated into a number of serological strains by means of absorption tests. Using eighty-five strains, he found six very distinct serological types.

Warren (1921) inoculated rabbits with doses of 1000 million gonococci and upwards at five-day intervals, and found that well-marked agglutinins were developed towards the strain inoculated. The best results were obtained by inoculating with a vaccine which had been heated to 65° C. for half an hour. Other rabbits were inoculated with emulsions of meningococci and *M. catarrhalis*, etc. From the results of his experiments he concluded that "the agglutination test does not serve to differentiate strains of gonococci into serological groups," but that agglutination to the gonococcus was specific. The highest titre which he obtained was 1 in 3200, after a series of inoculations.

Other Observations with regard to Agglutinins.—Bruck (1906) stated that when animals were inoculated with live cultures of gonococci the anti-serum produced was rich in agglutinins but poor in amboceptor (*i.e.* in complement-deviating substances), so that agglutination and complement-deviation did not run parallel.

Vannod (1906 and 1907), on the other hand, thought that both these anti-bodies developed equally together.

Wollstein (1907) found that inoculation with live gonococci produced a higher agglutination than when dead organisms were used. When extracts of gonococci were injected with or without live cocci very little agglutinin was developed. Her experiments with regard to amboceptor were not so definite.

Teague and Torrey (1907) and Torrey (1907) found that inoculation with different strains of gonococci produced specific agglutinins and specific amboceptor, and that these strains could therefore be distinguished by the agglutination and complement-fixation tests.

The serum of guinea-pigs and rabbits prepared by intra-peritoneal injection of gonococcal cultures agglutinated old cultures of gonococci more readily than young cultures.

Torrey (1908) states that the virulence of the gonococcus is increased by passage through animals, and that this renders the germs less agglutinable.

Watabiki (1910) states that there is no relationship between the complement-binding reaction and agglutination.

Debré and Paraf (1913) state that certain strains of gonococci are agglutinated by anti-meningococcal serum.

Pearce (1915) states that two principal types of gonococci may be recognised by suitable immunological tests, viz. by agglutination and complement-deviation. The two types correspond to the adult and infant types of gonorrhœa.

Field and Teague (1907) state that specific agglutinins are electro-positive, and that all the active principles of serum concerned in anti-reactions have a tendency to migrate towards the cathode under the influence of an electric current. Further, the proteid matter of serum is not amphoteric, but travels towards the cathode whether its reaction be acid, neutral or alkaline. The bacteria-agglutinin combinations may be disassociated by means of the electric current.

(b) **Precipitins.**—Bruck and Wildbolz, also Bruckner and Christéanu (1906), noted the presence of precipitins in the sera of animals immunised against gonococci, for when such sera were mixed with extracts of gonococci a faint precipitate was formed. Torrey (1907) carried out further researches on the subject.

Wollstein injected seven rabbits with living gonococci. Seven to eleven successive inoculations were given to each animal. The serum of all the animals showed the presence of agglutinins and amboceptor (complement-deviating substances), but only one serum from a rabbit which received nine inoculations gave any precipitin reaction. It gave this reaction with both gonococcal and meningococcal extracts, but only in dilutions of 1 in 10 to 1 in 20. It did not give any precipitate with extracts of the *M. catarrhalis*.

The precipitin reaction has been advocated by Dopter and Koch (1908) and Dopter (1909) as a means of differentiating the gonococcus from the meningococcus, but the experiments recorded by them were too few in number to justify the deduction of definite conclusions. Dopter carried the differentiation further by absorbing the precipitins.

Watabiki (1918) studied the question of precipitins in gonococcal infections and in anti-gonococcus serum. He also investigated whether the precipitin test will distinguish between the meningococcus and the gonococcus. He found that the serum of patients with gonorrhœa may contain specific gonococcal precipitins, but this seems to be the case only when the infection has been severe and has lasted for some time. The serum of patients suffering from typhoid fever or other non-gonococcal diseases does not contain gonococcal precipitin. The serum of rabbits injected with eight strains of gonococci contained precipitin, each one for all of the different gonococci, but in the case of two strains the extracts gave precipitates in lower dilutions with the serum of the other six rabbits than with the homologous sera, and their serum gave precipitates with the other six extracts in lower dilutions than the homologous extract. The serum of rabbits injected with the meningococcus, *M. catarrhalis*, and the colon bacillus gave no precipitates with gonococcal extracts. Apparently anti-gonococcus serum is not so rich in specific precipitins as in agglutinins and complement-fixing bodies, but the precipitin reaction distinguishes more definitely between gonococci and meningococci, as well as *M. catarrhalis*, than complement-fixation.

Calderola (1920) also carried out serological researches on the meningococcus and the gonococcus.

Thomsen and Vollmond (1920) succeeded in differentiating three types of gonococci in 26 strains from recent cases of urethritis in men.

The author has obtained the precipitin reaction on several occasions with the serum of human patients. The patients had been injected with large doses of detoxicated vaccine (see Chapter XXXI.) until they showed a very strongly positive complement-deviation reaction. The serum was mixed with a concentrated neutral solution of gonococci, and

allowed to stand in the ice-chest for a few days. The precipitate became very marked after about forty-eight hours.

(c) **Opsonins.**—By means of the opsonic index, Houston and Rankin (1907) claimed to be able to distinguish between different strains of meningococci. This method, however, according to their results would be quite useless for distinguishing the gonococcus from the meningococcus. Wollstein (1907) was unable to distinguish, by opsonic experiments, the gonococcus from the meningococcus.

Simonds and Baldauf (1909) state that the injection of heated bacterial cultures causes in from twenty minutes to four hours a leucopenia, followed in two or three days by a marked leucocytosis. The leucocytes usually return to normal in four days. The opsonic index shows little or no variation for the first few hours after the injection. The negative phase then sets in and lasts from two to four days. After this there is a gradual rise in the index, the maximum being reached on the fourth to eighth day. A gradual fall to normal occurs between the sixth and the twelfth days. The leucocytes are therefore evidently more sensitive to bacterial injections than the opsonic index.

(d) **Bacteriolysins.**—According to Torrey (1908) intra-peritoneal injections of living gonococci into guinea-pigs cause first a leucopenia which lasts about seven hours. This is followed by a leucocytosis in which the macrophages play a greater part than the polymorph leucocytes. He found, however, that the gonococci were largely destroyed before the leucocytosis set in. The cocci were actually disintegrated, due to the lytic action of the serous exudate. He found that fresh normal rabbit serum was strongly bactericidal for the gonococcus, and thinks that the lysis of the germ is probably brought about by an alexin. The natural lytic action of rabbit serum varied. Some normal sera were ten times as potent as others.

With regard to guinea-pigs which have been immunised, the bacteriolytic power of the serum was very strong. In these, the heart blood was sterile thirty minutes after an intra-peritoneal injection of living gonococci, and the peritoneal fluid was sterile in eleven hours. As early as ten minutes after the inoculation the gonococci were found in large clumps in the peritoneal cavity, and clumps were also found in the heart blood. This showed the presence of agglutinins. He maintains, however, that the destruction of the germs was due chiefly to the presence of bacteriolysins, since in thirty to sixty minutes the cocci were largely disintegrated and autolysed. The macrophages rapidly ingested the feebly staining disintegrated germs. When a guinea-pig dies from a very large injection of gonococci, the death is due to a fatal toxæmia occurring before the germs are destroyed by the alexin. He states that immunisation to the meningococcus and *M. catarrhalis* produces no immunity to the gonococcus.

Teague and Torrey (1907) found that in immunised animals there was a definite relationship between bacteriolysis and fixation of the complement. Thus strains A and C when injected separately into rabbits produced anti-substances which caused material lysis. The anti-serum to A lysed the germs of strain C, and *vice versa*. The same was true with regard to the complement-fixation test. The anti-sera to strains A and C did not react, however, with strains G and H, and *vice versa*. All the anti-gonococcal sera were slightly destructive to the meningococcus, but anti-meningococcal serum was not destructive to the gonococcus. Strains A and C produced more bacteriolysins to the meningococcus than the strains G and H.

Torrey (1908) states that bactericidal immune bodies are readily produced in rabbits by inoculation with the gonococcus and also with the meningococcus, but the serum immune to one strain of the gonococcus may be entirely inactive *in vitro* against another strain. All of the four inactivated anti-gonococcal sera tested were slightly bacteriolytic for a certain strain of meningococcus. On the other hand, an anti-meningococcus serum contained no bactericidal immune bodies against the four strains of gonococci. There was therefore a parallelism in the specificity of results obtained by the complement-fixation test method and the bactericidal *in vitro* experiments. The gonococci were

lysed and killed by mixing with the anti-serum for four and a half hours in the incubator at 37° C. He concludes that the experiments confirm his opinion expressed in a previous paper that the gonococcus group is heterogeneous. He also found that certain strains of the gonococcus were more susceptible to bacteriolysis than others, and thinks that this may explain the transient nature of some gonococcal infections.

Martin (1909 and 1910) also studied the bacteriolytic action of normal and immune sera of rabbits on both the gonococcus and meningococcus. He found that the technique was difficult because the gonococcus autolysed and died rapidly in normal salt solution, and also because variations occurred in the sera of normal animals from day to day. He states that Torrey used different amounts of rabbit serum with different strains and compared results on different days, and he considers that the fallacies which were possible thereby detract considerably from the value of Torrey's experiments.

Martin concluded from a large series of experiments that rabbits inoculated with living cultures of gonococci or meningococci developed bacteriolytic immune bodies in their sera. For the successful effect of these immune substances, however, the presence of complement was necessary, so that the bactericidal power of an anti-serum could be removed when the complement was destroyed by heating to 55° C. The inactivated bacteriolytic sera could be reactivated, however, by the addition of fresh normal serum containing complement, since their combination produced a marked bactericidal effect. The bacteriolytic immune bodies were relatively specific; thus a reactivated anti-gonococcal serum from the rabbit which had a marked bactericidal effect on the gonococcus had only a slight effect on the meningococcus.

Notes on the Aggressins.—Bail (1905) showed that sublethal doses of germs may become lethal under the influence of fluids containing "aggressins," which neutralise or destroy the natural protective substance of the animal.

Bail and Weil (1906) maintained that "aggressins" were formed chiefly, though not exclusively, by the body fluids acting adversely under the influence of the germs, and that they were formed first at the point of inoculation where the bacteria were proliferating most rapidly.

Wassermann and Citron (1905) and Citron (1906) were, however, able to obtain "aggressins" from bacterial extracts (without the interaction of the body fluids) by shaking up the cultures with distilled water. These latter observers therefore assert that the "aggressins" are not newly formed in the animal, but that they are merely dissolved bacterial substances which are akin to the toxins themselves.

Wollstein (1907) obtained gonococcal "aggressins" artificially by suspending a twenty-four-hours culture in 5 c.c. of saline containing a few drops of toluol. Under the influence of toluol, the germs autolysed overnight in the incubator at 37° C. The autolysate was placed in the ice chest. Later it was centrifugalised, and placed in the incubator to evaporate off the toluol. She found that if half a cubic centimetre of the extract was injected with a non-fatal dose of gonococci into a guinea-pig, death was caused in twenty-four hours. It appeared therefore that the extract might contain "aggressins." She states that the specificity of the aggressin is not limited to the homologous strain of gonococcus. Thus 2 c.c. of an emulsion of gonococci which did not kill a guinea-pig weighing 200 grammes, became fatal when 1 c.c. of its own extract was added. Conversely 2 c.c. of extract which was not fatal by itself was rendered lethal by the addition of 1 c.c. of the emulsion of the germs. Aggressins obtained from the meningococcus and gonococcus were not quite specific.

Paul and Lotti (1907) and others found that there was a certain quantitative but not qualitative specificity amongst the aggressins of different organisms. Bail and Salus, on the other hand, hold that the natural aggressins are strictly specific.

Wollstein (1907) found that vaccines of gonococcus cultures plus extracts of the germ, when injected into animals, produced an immunity against lethal doses of meningo-

coccus cultures, but the reverse, viz. injections of meningococci plus extract, did not give much immunity against the gonococcus.

Bruschettini and Ancaldo (1907) obtained a gonococcal aggressin from a gonococcal filtrate.

Warden (1915) states that numerous observations on intra-peritoneal lysis, such as occurs when gonococci are injected intra-peritoneally into guinea-pigs, have shown that the primary products of dissolution act as aggressins.

It would appear that aggressins and toxins are the weapons by which a germ is able to devitalise and attack its host, and there is no definite evidence so far to show that anti-substances are formed by the host against these poisons.

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CHAPTER XXVII

SHORT EXPLANATION OF THE COMPLEMENT-FIXATION TEST

THE complement-fixation test is founded on the discovery of Bordet (1898) and Bordet and Gengou (1901), and was first used for practical clinical purposes by Wassermann and Bruck (1906), who developed a reliable blood test for the diagnosis of syphilis. Now it would appear, from the more recent researches of the past few years, that a similar test may be applied eventually to the diagnosis of the majority of diseases.

The Principle of the Test.—Pfeiffer (1894) showed that when cholera germs were injected into an animal, anti-substances (bacteriolysins) were developed which could be detected in the serum.

Bordet (1898) found that a serum containing bacteriolytic anti-substances was rendered inactive by heating at 56° C. The addition, however, of fresh unheated normal serum had the effect of bringing back the bacteriolytic properties of the heated immune serum. Later, Bordet discovered that when the red corpuscles of one animal were injected into another species of animal, anti-substances (lysins) were developed in the latter to the red cells of the former. The anti-substances which had the power of dissolving the foreign corpuscles were termed "hæmolysins." He found that these hæmolysins were specific. A rabbit, for example, which had been inoculated with sheep's corpuscles, developed in its serum hæmolysins towards sheep's corpuscles only, and did not dissolve the corpuscles of other kinds of animals. Like the bacteriolysins, the hæmolysins were rendered inactive by heating to 56° C., but were again reactivated by the addition of fresh normal serum. To understand the next step in the discovery of the complement-fixation test, it is necessary to explain certain terms which have been developed in connection with it.

Antigen is the name applied to a foreign substance which when injected into an animal induces the formation of specific anti-substances. Thus bacteria and red corpuscles are antigens.

Amboceptor is the specific anti-substance developed as the result of one or more injections of antigen. Thus hæmolysins and bacteriolysins are amboceptors. Amboceptor is thermostable, *i.e.* capable of standing a temperature considerably over 56° C.

Complement is a substance present in fresh serum, and without which amboceptor is powerless to act. Complement is destroyed by heat at 56° C., so when an immune serum is heated to this temperature its amboceptor is no longer capable of causing lysis of the specific antigen (bacteria or corpuscles). This power, however, returns if fresh normal serum containing complement is added.

Thus it will be seen that for the successful action of amboceptor, whether hæmolysin or bacteriolysin, complement must be present.

Complement-fixation.—Bordet and Gengou found that if an antigen was mixed with fresh immune serum containing the specific anti-substance (amboceptor) and complement, and allowed to stand for some time, the complement disappeared. It was discovered that the antigen had entered into combination with the anti-substance, and thereby had used up the complement present in the serum. This phenomenon was

termed "fixation of the complement." More recent researches, *vide* Dean (1912), have shown that this is due to a colloid reaction. Antigen, amboceptor (anti-substance), and complement are all colloids. When antigen and amboceptor are brought into contact they unite to form a fine invisible precipitate, and this precipitate "adsorbs" the fine colloid particles of complement. The complement is then rendered inactive and is said to be "fixed" or "deviated."

The Complement-Deviation (Fixation) Test.—Suppose we wish to find out by this test if a person is suffering from gonorrhœa. We take the serum of that individual, and try to detect the presence of anti-substances to the gonococcus. If anti-substances (amboceptor) to the gonococcus are detected, this is strong presumptive evidence that the person must be suffering from the disease, and if these anti-substances are absent it indicates that the person is free or negative. We take the serum to be tested and heat it to 56° C. for ten minutes to destroy the complement. Then we add a known number of units of fresh complement (fresh guinea-pig serum previously tested to ascertain the amount of complement present, is used). We further add a small quantity of antigen (dissolved gonococci), and allow the mixture of serum to be tested plus complement plus antigen to stand for some time. If the serum contains specific anti-substance it forms a fine invisible precipitate with the solution of gonococci (antigen), and this adsorbs or fixes the complement.

Thus if we fail to detect complement in the mixture after it has stood for some time, anti-substance was present, so the serum gives a positive reaction to gonorrhœa, but if the complement does not disappear there was no precipitate, *i.e.* no anti-substance, and thus the test was negative to gonorrhœa.

The Method of detecting the Presence or Absence of Complement in the Mixture.—If we could see whether or not a fine precipitate were formed when the serum of an individual was mixed with a solution of gonococci, that would be sufficient to tell us that the person was positive or negative to the disease. We cannot, however, see this precipitate, so we have to detect its presence or absence by testing for the absence or presence of complement. Unfortunately we can only detect the absence or presence of complement by a round-about method, by the use of red corpuscles and specific hæmolysin to these red corpuscles. The red cells used are usually those of the sheep, and the blood serum of a rabbit which has been inoculated repeatedly with the former is used as the specific hæmolysin. The hæmolytic rabbit serum is heated to 56° C. to destroy the complement. It is then mixed with sheep's red cells. These cells do not dissolve, because there is no complement present. The cells, however, are said to be "sensitised," because, if complement is added to them, they would hæmolyse, due to the hæmolysin present.

Let us return once again to the test for gonococcal anti-substances in a human serum. We have made a mixture of human serum (heated) plus unheated guinea-pig serum (complement) plus antigen (dissolved gonococci), and this mixture has stood for some time. Now add sensitised sheep cells. If the cells dissolve, this shows that complement was present in the mixture; this means there was no precipitate, *i.e.* no gonococcal anti-substance, and so the reaction was negative to gonorrhœa. On the contrary, if the sheep's cells do not dissolve but settle to the bottom, this means that complement is absent, having been adsorbed by a fine precipitate due to a combination of antigen with gonococcal anti-substance in the human serum, and so the reaction was positive to gonorrhœa.

The complete test is more easily grasped if it is borne in mind that the whole procedure is a round-about method of testing for the presence or absence of complement, and that this in turn is an indirect method of detecting the absence or presence of a precipitate which is formed when antigen and anti-substance are brought together.

LITERATURE

See end of next Chapter, XXVIII.

CHAPTER XXVIII

HISTORICAL AND CRITICAL REVIEW OF THE RESEARCHES ON THE COMPLEMENT-FIXATION TEST FOR GONORRHŒA FROM THE BEGINNING UNTIL THE PRESENT TIME

MÜLLER and Oppenheim (1906) were the first to employ this blood test in the diagnosis of gonorrhœa. They used as the antigen an extract of gonococci, and obtained a positive result with the serum of a patient suffering from gonococcal arthritis. The serum of another patient suffering from arthritis due to other causes gave a negative reaction.

Bruck (1906) demonstrated that the serum of rabbits which had been immunised against the gonococcus deviated complement in the presence of a watery extract of gonococci. He also obtained positive reactions with two out of six cases of salpingitis, one out of a number of cases of epididymitis and urethritis, and also in a case of recurrent iridocyclitis. He was unable to detect any such complement-deviating substances in normal sera.

Teague and Torrey (1907) state that the serum of a rabbit A immunised against a given strain of gonococcus A, deviated complement in the presence of antigen prepared from strain A, but not with that made from gonococcus G or H. *Vice versa* the serum of rabbits G or H immunised against gonococcus G or H would give positive reactions with extract of G or H gonococcus, but not with A. As a result of their work on these lines they separated the gonococci obtained from ten different sources into three groups. They concluded that it was necessary to use several different strains in the complement-fixation test, and that in treatment with anti-serum, the serum should be one which has been rendered immune to several different strains, *i.e.* polyvalent. In their tests they kept a constant amount of complement and antigen, and varied the amount of the serum. They prepared their antigen by emulsifying a twenty-four to forty-eight hours' slope culture of the gonococcus in 5 c.c. of sterile distilled water, and then heating at 60° C. for half an hour. The emulsion was then shaken up for forty-eight hours in a shaking machine and finally centrifugalised, the supernatant fluid being used. This extract was never quite clear, and they never used it more than three days old. Guinea-pig complement was employed, and goat corpuscles sensitised with anti-goat serum. With the sera of eight normal persons the test gave a negative result with eight different strains of gonococci. Positive reactions occurred chiefly in chronic cases of gonorrhœa, and they obtained negative results in two acute cases. They stated that anti-meningococcus serum did not give positive reactions with gonococcus extracts, except in some cases.

Vannod (1906) tested by this method the serum of rabbits immunised against gonococci and meningococci, and found that by it the anti-gonococcal and anti-meningococcal sera could be distinguished from each other. For antigen he used 0.1 c.c. of a well-shaken and centrifugalised emulsion of gonococci. Guinea-pig serum 0.1 c.c. was used for complement, and the immune serum was tested in amounts which varied from 0.01 c.c. to 0.001 c.c.

Wollstein (1907) applied the complement-fixation test to the serum of four rabbits immunised against the gonococcus. She prepared her antigen by emulsifying a twenty-

four-hours culture of the gonococcus in 5 c.c. of saline containing a few drops of toluol to encourage rapid autolysis. This emulsion was kept in the incubator overnight at 37° C., then placed in the ice-chest; later it was centrifugalised, and again placed in the incubator at 37° C. to drive off the toluol. The supernatant fluid was used as the antigen. In the test she used a hæmolytic system consisting of hen's red cells, sensitised with anti-hen serum, and she titrated the immune serum and the antigen successively against double the smallest dose of complement which was bound by each. The sera of the four rabbits which had been inoculated with gonococcus extract gave positive results. One serum (diluted 1 in 50) deviated the complement in the presence of 0.1 c.c. of gonococcal extract, and also with 0.1 c.c. of meningococcus extract. Strict specificity between the gonococcus and meningococcus was therefore lacking. Control extracts (or antigens) made with *M. catarrhalis*, streptococci, *B. typhosus*, and two varieties of dysentery bacilli failed to produce any deviation of complement with anti-gonococcus serum, and conversely, anti-typhoid serum failed to deviate with a gonococcus extract. She was unable, however, to distinguish between the gonococcus and meningococcus by this method.

Meakins (1907) obtained positive results with the test in two out of three cases of gonococcal arthritis, and in cases of gonococcal prostatitis and chronic urethritis.

Krumbein and Schatilloff (1908) considered that the complement-fixation reaction was specific for the meningococcus and for the gonococcus with their respective sera, but Arkwright (1912) found this method in no way superior to agglutination as a means of distinguishing the two organisms.

Watabiki (1910) employed a gonococcal antigen made according to the prescription of Teague and Torrey. Gonococci from eight sources were used, a separate antigen being prepared from each strain and always freshly prepared. He also used a fixed amount of complement with varying amounts of the serum to be tested. One normal serum in a quantity of 0.1 c.c. gave a positive reaction with six of the extracts, but two others gave negative reactions with all eight of the extracts; no normal serum gave a reaction in a less amount than 0.1 c.c. Two out of three cases of chronic or sub-acute gonorrhœa gave positive reactions with seven out of the eight strains, using 0.05 c.c. serum; but two cases of acute gonorrhœa were negative. Control sera of patients with other illnesses always showed negative reactions. The reactions given by the serum of animals immunised against the eight strains of gonococci confirmed the conclusions of Teague and Torrey as to the multiplicity of strains of gonococci, the eight strains being divided into two groups by means of this test, but, unlike these observers, he found that the difference was only comparative. He further states that anti-meningococcus sera did not give a positive reaction with his gonococcus antigens except in a few cases.

Nencioni (1910) carried out the test in 33 gonorrhœal subjects with the following results:—Three out of 19 urethritis cases gave a weak positive, and 1 gave a positive. Out of 7 epididymitis cases, 2 were negative, 4 were weakly positive, and 1 definitely positive. Out of 7 arthritis cases, 3 were negative, 2 weakly positive, and 1 strongly positive.

Martin (1910) employed the method described in the *Jour. of Hygiene* (1906, vol. vi. p. 267), using constant amounts of antigen and serum, and varying amounts of guinea-pig complement. The antigen consisted simply of gonococcal and meningococcal emulsions in salt solution, standardised to a definite density and heated to 80° C. for fifteen minutes. The amounts used for the test were 0.1 c.c. of emulsion (antigen) and 0.05 c.c. of the serum. The volumes were made up to 0.5 c.c. with saline solution, and then guinea-pig serum (complement) was added in increasing amounts. The mixtures were incubated for one and a half hours before adding the test one c.c. of sensitised ox red blood corpuscles. In his experiments Martin employed rabbits which had been injected with cultures of gonococci and meningococci. He found that the immune sera alone did not absorb any appreciable amount of complement, but that the emulsions (antigens) of meningococci and gonococci alone absorbed four and three minimum hæmolytic doses respectively. On the other hand, the combination of each of these emulsions with their specific immune

sera deviated thirty doses in the case of the meningococcus and ten in the case of the gonococcus, while the combination of meningococcus emulsion and anti-gonococcal serum and *vice versa* deviated six and four doses respectively. These experiments indicated the presence of both specific and group immune bodies in the anti-sera. He agrees with Teague and Torrey, Vannod and Watabiki, that the test can be of service in differentiating between the gonococcus and the meningococcus.

Torrey (1910) states that gonococcus antibody begins to be eliminated from the blood of immunised rabbits about ten days after the last inoculation, and continues to be eliminated from the tenth to the fiftieth day.

Colombo (1911) published a series of observations on complement-fixation with regard to the meningococcus and gonococcus, and was unable to find any specific difference between them. He used almost entirely polyvalent sera.

Dembska (1911) tested the serum of 100 females with gonorrhœal affections of the appendages, etc., and came to the following conclusions :—

(1) Early cases of gonorrhœa with urethritis, Bartholinitis, etc., gave only weak reactions.

(2) Recent affections of the appendages with peritonitis gave definite positive reactions.

(3) Cases in which the tubal affections had existed for more than two weeks gave a markedly positive reaction.

(4) When a streptococcal antigen was used, the sera in all cases gave completely negative results.

Schwartz and McNeil (1911 and 1912) contributed much valuable work on the application of complement-fixation to the diagnosis of gonococcal infections. They tested the sera of 324 patients of both sexes suffering from gonorrhœa and other diseases. Having confirmed the conclusions of Teague and Torrey as to the multiplicity of strains of gonococci, they considered that for diagnostic purposes the best antigen would be a mixture of several different strains. They used therefore in their tests a compound antigen of gonococci obtained from nine to twelve different sources, and prepared after the method of Teague and Torrey. The amount of antigen employed in the test was one half the amount which just failed to deviate a fixed amount of complement when incubated with a normal serum. Guinea-pig serum was used as complement, the amount being 0.15 c.c. of a 1 in 10 dilution. The amount of tested serum was 0.15 c.c. ; after incubation of serum, complement, and extract for one hour at 37° C., 0.05 c.c. of a 5 per cent suspension of sheep's cells was added, with 0.5 c.c. of a suitable dilution of anti-sheep-cell amboceptor.

Their results were briefly as follows :—

<i>Acute gonorrhœa</i> of 3 to 21 days' duration	1	positive,	5	negative.
<i>Chronic gonorrhœal urethritis</i> , 7 weeks to 10 years' duration	27	„	9	„
<i>Chronic prostatitis</i> with gonorrhœal history	17	„	8	„
<i>Sterility</i>	1	„	2	„
<i>Epididymitis</i>	2	„	1	„
<i>Clinically cured gonorrhœa</i>	22	„	29	„
<i>Gonococcal arthritis</i>	14	„	0	„
<i>Arthritis of doubtful gonorrhœal origin</i>	4	„	3	„
<i>Gonorrhœa in women</i> (gynæcological cases)	23	„	6	„
<i>Miscellaneous cases with no sign or history of gonorrhœa</i>	0	„	20	„
<i>Normal cases who had never had gonorrhœa</i>	0	„	16	„

These authors state that the greater the number of strains present in the antigen the greater is the number of positive reactions obtained, also that the test is absolutely specific. When the disease was limited to the anterior urethra they were unable to get positive results, and strongly positive results were only obtained after the fourth week of infection. A positive reaction, moreover, did not disappear until seven or eight weeks

after cure. In 62 cases of chronic prostatitis giving a history of gonorrhœal infection within three years a positive reaction was obtained in 54.8 per cent. In 165 cases regarded as clinically cured a positive test was obtained in 13.2 per cent. With regard to females, cases of vaginitis did not give a positive reaction. Positive results were only obtained when the disease affected the cervix or higher up. All cases of gonorrhœa which had been treated with vaccines and examined some months afterwards, gave uniformly negative results.

The work of Schwartz and McNeil has been confirmed by Schmidt (1911) and Keyes (1911), and more or less similar results were obtained by Merkuriew (1911), Lenartowicz (1912), Gradwohl (1912), and also by Foix and Salin, and others. Keyes injected gonococcal vaccines into himself, and failed to get a positive complement-fixation reaction with his serum.

Swinburne (1911) contributed a paper on the subject, but unfortunately the author has not been able to obtain access to his work.

Schmidt (1912) recorded the results of the complement-deviation test in 103 patients in private practice. Thirty-four cases had never had gonorrhœa and were clinically free from the disease. In all of these the test was negative. In three early cases of gonorrhœa, tests made in the second week were all negative. Of 24 chronic cases, 17 were positive and 7 negative. Nearly all of these had posterior adnexal trouble, and a few had epididymitis. In all, gonococci were found within thirty days previous to the test.

Of 42 cases examined mostly for conditions other than gonorrhœa, and with a history of this disease from one to thirty years previously, 5 gave positive results and 37 negative. Schmidt concluded that a negative test was a good indication of cure, and that cases which are infective for a long period of time are less common than was formerly supposed.

Gardner and Clowes (1912) give the results obtained in 106 cases.

Of these 23 were + + +, 15 + +, 23 +, and 37 -.

Of the 23 triple positive cases, 18 out of 20 examined showed gonococci microscopically.

Of the 15 double positive cases, 9 out of 13 examined showed gonococci microscopically.

Of the 23 single positive cases, 11 out of 17 examined showed gonococci microscopically.

They consider + + + and + + reactions as diagnostic.

Smith (1912) and Weston (1912) contributed further papers on the subject.

Vandegrift (1912) describes a case of gonorrhœal chorioiditis, complicated by chronic prostatitis, with the presence of gonococci in the smear preparations. A strongly positive test was obtained. Under the influence of vaccines both the prostatitis and the eye condition subsided. A month after the last findings of gonococci in the prostatic secretion, the blood test was weakly positive, and after another month, by which time the eye condition had cleared up, the test was completely negative.

Schwartz (1912) reported on a series of 110 cases of joint disease of varying etiology. In 17 cases in which gonococci were present in the urethral or vaginal pus at the time of the blood test, 16, or 94.1 per cent, gave a positive result. In his opinion a positive reaction is an absolute indication of gonococcal infection somewhere in the body, but should not be expected earlier than about the beginning of the fourth week from the onset of the infection. He considers the test very valuable in patients with obscure rheumatic conditions. One of his cases suffered from two infections, viz. acute rheumatic fever and gonorrhœa.

O'Neil (1912) published the results of 256 complement-fixation tests for gonorrhœa at the Massachusetts General Hospital. The antigen used was made from a mixture of cultures of gonococci obtained from different patients. The twenty-four-hour surface growths on hydrocele agar were suspended in normal salt solution and allowed to disintegrate for some days or weeks in the ice-chest. The technique of the test proper is not given. The following is a short *résumé* of the results, which are given in detail in the original paper :—

	Cases.	Positive.	Negative.
Cases with gonorrhœal history which were clinically uncured . . .	109	95	14
Cases of gonorrhœa in which the cure was doubtful clinically . . .	27	9	18
Cases where the diagnosis of gonorrhœa was doubtful . . .	16	5	11
Cases with gonorrhœa on examination at the time of the test (history of gonorrhœa in most cases) . . .	52	9	43
Cases suffering from other diseases from the general wards . . .	35	11	24
Cases with no history of gonorrhœa . . .	17	0	17
Totals . . .	256	129	127

Of these cases 48 were females (lower genital tract involved); 22 gave a positive test. In addition there were 20 cases with pelvic troubles. Of these 13 gave a positive reaction. Two cases of iritis with a gonorrhœal history gave negative reactions.

Lederer (1912) in conjunction with Hecht obtained positive reactions with the serum of gonococcal cases, using "arthigon" (a commercial gonococcal vaccine) as antigen.

Brahns (1913) also tested the sera of 140 cases of gonorrhœa and 32 normal persons, using "arthigon" as the antigen. All the normal sera gave negative results, but he only obtained 16 positive reactions out of 137 cases of complicated gonorrhœa. He considered, therefore, that "arthigon" was much inferior as an antigen to the polyvalent emulsions of gonococci used by Schwartz and McNeil, Lenartowicz, and others.

Van Saun (1912) attempted to ascertain whether different types of culture media employed in growing the gonococcus had any effect in altering the antigenic value of the organisms. Her experiments were inconclusive. She states that a good growth seems to be favourable for good antigenic properties, but that a good growth does not always guarantee a good antigen.

Arkwright (1912) immunised rabbits with three strains of meningococci and five strains of gonococci, by injecting them intravenously at intervals with increasing doses of the cocci. He obtained in this way eight monovalent anti-sera, three anti-meningococcal and five anti-gonococcal. He also prepared eight corresponding antigens, by emulsifying each of the growths produced on ascitic agar with 10 c.c. of salt solution. After adding a few drops of chloroform and shaking, the emulsion was left at room temperature for three or four days. The extract was then centrifuged before use. It was found that if the deposit from the last centrifuging was again made up to the original volume with salt solution and left for a further period of two to three days, a second extract as good as the first could be obtained, and again, by repeating the same process, a third and even a fourth extract could sometimes be obtained of almost undiminished value for complement-fixation experiments. The extract was diluted eight, or in some cases sixteen times, before use, and the specific meningococcal or gonococcal serum was diluted eight times. Some experiments were made in which falling doses of extract were used with a constant dose of specific serum, and other experiments in which the dose of extract was constant, but the dose of serum decreased in the successive tubes. The results yielded by the two methods were on the whole alike. The hæmolytic system used in the test consisted of sheep's corpuscles, rabbit-*v*-sheep serum, and guinea-pig complement. As the result of his experiments he drew the following conclusions:—

(1) Meningococcal sera produce complement-fixation as readily with some gonococcal extracts as with extracts of some strains of meningococcus, whereas no reaction is obtained with some heterologous meningococcal extracts.

(2) A monovalent serum usually reacts better with an extract of its homologous coccus than with extracts of other strains of meningococcus or gonococcus, but a gonococcal extract sometimes gives a better reaction with a meningococcal serum than the homologous extract does.

(3) Gonococcal sera and extracts are on the whole more potent than those prepared from meningococci as regards complement-fixation.

(4) No satisfactory distinction between meningococci and gonococci can be demonstrated by means of complement-fixation tests.

Irons (1913) stated that complement-fixation was the most satisfactory method of measuring the antibody content of a patient's serum. The amount of gonococcal antibody underwent marked fluctuation, apart often from any clinical explanation, and the opsonic properties of the serum behaved similarly.

Owen and Snure (1913) in a series of tests got much the same results as those obtained by Schwartz and McNeil. They state that the test gives a very high percentage of positive results when gonococci are present, except in the very early and acute stage. The test often points to the presence of gonococci when none can be found microscopically. They never got a positive test in a non-gonorrhoeal patient. Cured cases became negative in five to eight weeks, and the persistence of a positive reaction beyond that time indicates that live gonococci still exist in the patient. The test showed that from 10 to 20 per cent of clinically cured patients were still infectious. Tests performed at random on a large number of individuals gave from 7 to 20 per cent of positive results. They urge that the Wassermann and gonococcal complement-fixation test should be done before marriage in the case of all persons who have suffered from syphilis or gonorrhoea.

Hastings (1913) contributed a paper on the complement-fixation tests for the streptococcus, gonococcus, and other bacteria in cases of deforming arthritis and arthritis deformans. He prepared his antigens according to the method of Teague and Torrey, and used them in the tests at a strength corresponding to 100 million organisms per c.c. In 24 cases the tests were negative with all his antigens. In 4 cases of typical arthritis deformans and 3 cases of infective deforming arthritis a positive reaction was obtained with the gonococcus antigen. In 3 cases of arthritis deformans he made cultures from the prostatic secretion after massage of the gland, and obtained in each a growth of streptococci. In 2 of these cases autogenous vaccines were made from the cultures, and these vaccines caused marked improvement in the disease. He concludes that some cases of arthritis deformans are infective in nature, and that the infecting germ may be a streptococcus or a gonococcus.

Smith (1913) published a short account of the results obtained in 25 cases of gonococcal vulvo-vaginitis in children. Eleven out of 12 clinically positive cases gave a positive complement-deviation reaction, and positive reactions were obtained in other 4 cases where the clinical evidence of the disease was doubtful. In the remaining 10 patients a negative result was obtained; 7 of these were undoubtedly cured clinically, but in the other 3 the cure was uncertain.

McDonagh and Klein (1913) used the complement-fixation test as a guide to the administration of gonococcal vaccines. Their antigen was an emulsion of a forty-eight-hour growth of recently isolated gonococci on ascitic or pleuritic fluid agar. The emulsion was standardised to a strength of 300 to 500 millions per cubic centimetre. Working with fifteen different strains of gonococci, from each of which an antigen was prepared, they found that different strains varied in their deviating properties with anti-gonococcal serum, and that those strains which gave the best deviation with positive sera had a greater immunising value as vaccines. The proportion of reagents used in their test were:—Complement, one volume (0.1 c.c.) containing three minimum hæmolytic doses; serum, one volume of 1 in 5 dilution; and antigen, one volume of the lowest dilution which allowed complete hæmolysis when tested with a normal serum.

Rockwood (1913) states that out of 193 tests he never got a positive reaction where the absence of gonorrhoea was certain. Two cases in which the urethral infection had been present for more than four weeks, and in which Gram-negative diplococci were found, gave a negative test.

In over 80 per cent of cases in which gonorrhoea was indicated clinically or bacterio-

logically or by history, he got a positive reaction. Of patients clinically cured, over 80 per cent gave a negative test, and in no case where a negative reaction was obtained did any relapse occur. With regard to the effect of vaccines, two of his cases, which had 300 million gonococci injected in the course of six weeks, gave a negative reaction.

In a later paper published in the same year he states that out of 200 cases of early acute urethritis, none showed any evidence of antibodies before the third week. So that if the reaction is positive before that time it indicates the relapse of an old gonorrhoea.

Cases of chronic urethritis almost invariably gave a positive reaction. In a total of 500 tests, only 5, or 1 per cent, were negative. In these 5, Gram-negative diplococci were found in the smears, but he suggests that they may not have been gonococci. In a series of 55 cases of chronic urethritis where no gonococci could be found, but with a history of gonorrhoea six months to two years before, 33, or 60 per cent, gave positive reactions.

In a series of 122 cases clinically cured, 19, or 15 per cent, gave positive results. He states that a period of several weeks is required for the elimination of the antibody after cure. Out of a series of 42 cases of epididymitis and prostatitis 75 per cent were positive. No gonococci could be found in the other 25 per cent where negative tests were obtained.

He states that the test should be applied before vaccines are given, and that two or three months should elapse after vaccine treatment before one can apply the test to determine whether a cure has been obtained. Cases of vulvo-vaginitis gave a negative test, but when the disease had spread beyond the vagina, a large percentage of positive results were obtained.

He employed the technique used by Schmidt (1911). For antigen he used the material prepared by Parke Davis & Co., and containing ten or more strains of gonococci. This antigen is prepared from cultures grown on ascitic agar. The surface growths are emulsified in salt solution, and then macerated by shaking for a long time. Finally, the material is filtered through a porcelain filter, and a small quantity of trikresol is added to the filtrate as a preservative.

McNeil (1913) states that in cases of acute anterior urethritis in the male and acute vulvo-vaginitis in the female, a positive reaction is practically never obtained; but shortly after the infection of the posterior urethra in the male, and the cervix and Bartholin's glands in the female, the serum begins to give a positive result. A positive reaction usually persists for six to eight weeks after cure. He does not think it is safe to assume a cure on a negative result, except after two or three consecutive negative reactions.

With the sera of 8 cases of vulvo-vaginitis of from one to three years' standing, he obtained the following results:—

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Finkelstein and Gershun (1913) employed an anti-sheep hæmolytic system, and incubated their tubes for two hours before adding the sensitised sheep cells. They obtained the best results with Uhlenhuth's anti-formin gonococcal antigen. This anti-formin antigen was first introduced by Merkuriew. The authors found that it was vastly superior to watery extracts of the gonococcus. With the former they obtained positive results in 23.5 per cent of acute cases of gonorrhoea and in about 100 per cent of chronic cases, whereas with the watery extracts they only obtained 13.7 per cent positive results in acute cases, and 44.3 per cent positive reactions in chronic cases.

Thirty-four acute cases were tested, and of these, 8, or 23.5 per cent, gave a positive reaction. Of 58 chronic or subacute cases, including chronic urethritis, epididymitis, arthritis, and pelvic disease in women, strongly positive reactions were obtained in 72.5 per cent, and weakly positive in 27.5 per cent. In cases of acute arthritis no reaction was obtained until the tenth day of the disease. With a streptococcus antigen, negative results were obtained in 25 cases of gonorrhoea tested. Thirty-one cases, non-gonorrhoeal, including patients with syphilis, soft sore and tuberculosis, all gave negative results with gonococcal antigen. They state that the administration of gonococcal vaccine produces a progressive strengthening of the antibody content in the serum.

Harrison (1914) attempted to make the test more delicate by reducing the amount of complement and increasing the antigen. He used an extract containing three or more strains of gonococci grown on Wertheim's human serum agar. The saline emulsion of the mixed organisms was shaken for an hour in contact with broken glass, and not centrifuged. He found, like McDonagh and Klein, that the antigenic value of the extract deteriorated on keeping, even although it was kept in a frozen condition. As a preliminary to the test he titrated the antigen in varying dilutions against 1·3 minimum hæmolytic doses of complement in the presence of saline instead of serum. After forty-five minutes' incubation, sensitised cells were added, and the reading taken after another forty-five minutes' incubation. One volume of twice the dilution of antigen, which slightly interfered with lysis, was used in the test proper. He used guinea-pig complement, and the hæmolytic system consisted of a 3 per cent suspension of sheep's cells sensitised with ten hæmolytic doses of amboceptor. The serum to be tested was heated at 55° C. for half an hour to destroy its own complement.

The test proper consisted of serum (to be tested) 1 in 10, one volume.

Complement 1·3 M.H.D., one volume.

Antigen in dilution ascertained by titration, one volume.

After shaking, the mixture was incubated for forty-five minutes in a water bath at 37° C., and he then added sensitised sheep red cells, one volume.

Controls.—Each serum was incubated with complement, in the same amount as in the test, and with one volume of saline in place of antigen. A normal and a positively acting serum were included in each batch of tests, and the readings were taken as soon as the normal serum control showed complete hæmolysis.

The following results were obtained with 121 specimens of serum from 88 persons, normal and suffering from gonococcal or other affections :—

(a) Acute or subacute urethritis, 20 cases—13 positive and 7 negative.

These cases were first attacks, without complications (except in 3 positive cases, in each of which there was a peri-glandular infiltration a centimetre behind the glans penis).

(b) Chronic urethritis, 6 cases—4 positive and 2 negative.

(c) Epididymitis, 15 cases—13 positive and 2 negative.

(d) Prostatitis, 5 cases—all positive.

(e) Arthritis and synovitis, 6 cases—4 positive and 2 negative.

(f) Gonorrhœa supposed to be absent, 35 cases—1 positive and 34 negative.

It should be noted that he obtained by his technique a much higher percentage of positive reactions in recent acute cases than any other previous workers.

Kolmer and Brown (1914) obtained the following results with 92 sera tested :—

	Positive.	Negative.	Percentage positive.
Urethritis (one to four weeks) (positive results uncommon under four weeks)	6	7	46·1
Urethritis (four to eight weeks)	3	2	60
Urethritis (eight to twelve weeks)	3	2	60
Urethritis (over one year)	19	10	65·5
Arthritis (probably gonorrhœal)	5	1	83·3
Vaginitis (children)	5	5	50
Chronic salpingitis	4	2	66·6
Controls (normal)	0	7	0
Syphilis	1	8	11·1
Chancroids	0	2	0

The highest percentage of positive results (83 per cent) occurred in cases of arthritis considered clinically as possible gonococcal infections. They state that the test is very

valuable as an aid to diagnosis in obscure joint conditions, in inflammatory pelvic diseases of women, and in cases of vaginitis in children. It is also most useful in deciding whether or not a given case of urethral infection is cured, or still harbours foci of living gonococci. In their opinion the test is not generally as satisfactory as the Wassermann test in syphilis, because the quantity of antibody produced in gonorrhoea is much smaller, unless grave and widespread metastases exist. They also state that the fixation of complement by bacterial amboceptor and antigen is not so marked as that occurring with the syphilis "reagin" and a lipoidal extract. In a comparative study of a number of sera tested with both the anti-sheep and the anti-human hæmolytic systems, slightly better results were secured with the latter. They maintain that gonococcus antigen, to be of any value, must be polyvalent, and they found that an antigen composed of a simple suspension of gonococci in saline solution yielded 11 per cent better reactions than filtrates of the germs. They consider, therefore, that the bacterial protein, apart from the endotoxin, aids in the antigenic effect. Alcoholic extracts of gonococci, in their opinion, made extremely poor antigens.

With the use of antigens of staphylococci, streptococci, and diphtheroid bacilli isolated from cases of prostatitis, they obtained positive reactions in about 9 per cent of cases of chronic gonococcus infections. This would seem to indicate that these secondary organisms may play an active rôle in gonorrhoea. With an antigen of the *Micrococcus catarrhalis* a positive reaction occurred in 5 per cent of cases, showing that this organism may be likewise active in chronic urethritis.

After a series of further tests made on anti-gonococcus and anti-meningococcus sera with antigens of gonococci and meningococci, they concluded that a biologic relationship existed between them. They found that while their respective amboceptors were most specific for their own antigens, in lower dilutions this specificity was not so apparent. Their results constituted, therefore, another example of "group" reaction, similar to those occurring with the groups of streptococci, diphtheria bacilli, spirochaetes, etc.

Sharp (1914) studied 27 cases of vulvo-vaginitis in children, varying from fifteen months to thirteen years old. Of these very few showed typical gonococci in Gram-stained smears, but by careful cultivation on plates and on slope tubes he was able to isolate the gonococcus in all but 5. Most cases had other secondary organisms as well, such as staphylococci, diphtheroids, etc. He also carried out the complement-deviation test, using as antigen the strains of gonococci which he had isolated. Only 9 of the 27 cases gave a positive reaction. He states that the positive results were obtained chiefly from cases of three months' duration or less. The negative results were obtained largely in the cases of longer standing. He does not agree with Smith that a negative test is a sign of cure, since he cultivated the gonococcus from 5 cases which gave a negative complement-fixation reaction at the time, and 3 of these had still quite an active discharge. In his series of 27 cases he obtained the following results by different methods :—

- (1) By cultural tests 22 were positive, gonococci being isolated.
- (2) By complement-fixation 9 were positive.
- (3) By the cutaneous reaction 10 were positive.
- (4) By microscopic examination of smears 5 were positive.

He considers that gonococci are present so long as the discharge continues, but the complement-fixation reaction seems to go after three months. He found that the strains of gonococci which he isolated from his cases were more resistant to heat than the ordinary gonococcal strains isolated from adults. Some of his vulvo-vaginitis strains survived a temperature of 42° C.

McNeil, A. (1914), contributed a paper on the subject, but the author has been unable to gain access to his work.

Smith, G. G. (1914), in a further paper on the "Value of the Complement-fixation Test in the Treatment of Gonococcus Vulvo-vaginitis," states that a weakly positive test

cannot be considered evidence that infection is still present. A negative test, on the other hand, appears to be proof of its absence. Of 7 patients who had weakly positive tests a year ago, 5 remained well clinically; of these, 2 now gave negative reactions, 1 was still moderately positive, and 2 weakly positive. The other 2 still showed some vaginitis, in which, however, gonococci could not be found. He claims that long and persistent treatment is necessary to obtain a successful cure, and that the blood test should be employed regularly. A small proportion of cases, after complete eradication of the gonococcus, are liable to attacks of non-gonorrhœal inflammation for some time.

Thomas and Ivy (1914) published a total of 204 cases tested. They used an antigen prepared as follows:—Take a forty-eight hours' culture on blood agar and wash off the growth with sterile distilled water. Shake for one hour, and then allow to autolyse for twenty-four hours at 37° C. Finally heat in a water bath at 60° C. for half an hour. They were satisfied that a hexavalent antigen gives more positive results than a trivalent antigen, which in turn is better than an antigen containing one strain only. They state that Schwartz and McNeil used minimum quantities of material in their tests, viz. 0.02 c.c. serum, 0.3 c.c. and 0.15 c.c. antigen, 0.1 c.c. complement, and 0.1 c.c. sheep cells. They, however, used larger quantities of the materials but much less antigen.

They draw the following conclusions from their results:—

(1) A positive reaction is invariably reliable, and always denotes the presence of a focus of gonococci.

(2) A negative test may fail to denote the presence of the disease, especially in the acute and subacute stages, when limited to the urethra, and the test is never positive when the disease is confined to the anterior urethra or vagina alone.

(3) The test is absolutely specific.

(4) A positive reaction was obtained in 21.05 per cent of patients clinically cured. Such patients should not be discharged until a negative reaction is obtained.

(5) They often got a positive result in patients who denied gonorrhœa, but who had suspicious lesions present.

(6) In only 9.09 per cent of cases of acute and subacute antero-posterior urethritis did they get a positive result. The earliest appearance of a positive reaction in primary attacks of antero-posterior urethritis occurred in the sixth week.

(7) In a number of cases of chronic recurrent arthritis the test was invariably positive. Many of these cases had prostatitis.

(8) In 52.08 per cent of cases of chronic prostatitis a positive reaction was obtained.

(9) Two-thirds of all stricture cases gave a positive test.

(10) In epididymitis 87.5 per cent were positive. One hundred per cent of cases of five weeks' duration were positive.

(11) In cases of arthritis, undoubtedly gonorrhœal, 100 per cent were positive.

(12) In the diagnosis and differential diagnosis of pelvic diseases in women the test is destined to play an important rôle. They were unable, however, to obtain any positive reactions in uncomplicated cases of urethritis, vulvo-vaginitis, and Bartholinitis. The infection must ascend to the level of the uterus before a positive test is obtained.

(13) Inoculations with gonococcal vaccine may produce a positive test, but patients treated by vaccine proved to be negative one year later.

(14) The complement-fixation test is simpler than a bacteriological examination, and gives more positive results.

(15) The test will soon be recognised as being as indispensable as the Wassermann, and it should always be adopted for the marriage test.

Thomas, Ivy, and Birdsall (1914) state that on rare occasions polyvalent antigens prepared from meningococci, pneumococci, streptococci, and *Bacillus coli* have given a positive complement-deviation reaction in cases of gonorrhœa. They do not consider, however, that this jeopardises the specificity of the gonococcus antigen, since it is explained on the basis of the supervention of a mixed infection in gonorrhœa.

In 10 per cent of cases a weakly positive result was obtained with polyvalent *Micrococcus catarrhalis* antigen. They explain this by assuming that the latter organism occasionally exists in the urethra along with the gonococcus, and that occasionally a catarrhalis strain may be included in a polyvalent gonococcal antigen.¹

Lanford (1914) published an article on the diagnosis of gonorrhœal infections by fixation of the complement. The author has not been able to gain access to his work.

Jones and Simons (1914) maintain that the complement-deviation test in gonorrhœa is even more specific than the Wassermann test for syphilis. It is of the greatest value in chronic cases, and complicated cases of gonorrhœa gave 100 per cent of positive reactions. No non-gonorrhœal case had given a positive result. They conclude that a negative blood test is advisable in a candidate for matrimony, if he has a history of previous gonorrhœal infection, even although apparently cured.

Corbus (1914) treated cases of gonorrhœa and its complications with injections of anti-gonococcic serum, and controlled the results by means of the complement-deviation test. He states that a negative reaction after two or three months indicates a complete cure. He got the best therapeutic results with the anti-serum in those cases which showed a strongly positive blood test.

Uhle and Mackinney (1915) published a paper based on a study of 155 complement-deviation tests, in which the sera of 141 individuals were tested by each of four competent serologists. One sample was sent to each serologist. Of the 141 cases, 15 were normal controls who never had gonorrhœa, 37 suffered from other diseases, and all denied ever having had gonorrhœa, and presented no clinical evidence of infection. The remaining 87 had, or had previously had, gonorrhœa. With regard to the 15 normal sera, only one laboratory B reported all negative. The other three laboratories reported from 6.6 per cent to 13.3 per cent as positive. In the next group of 37 cases, laboratory B reported all negative, the other three laboratories gave 13.5 per cent to 35.1 per cent as positive. Of 18 cases clinically cured for over five years, the four laboratories agreed in a negative report in 8. Of 11 cases with acute gonorrhœa of less than four months' duration, all the laboratories agreed in a negative result in 3 cases. With regard to 30 cases of chronic urethritis, all four laboratories gave negative returns in 11 cases. There were 6 acute cases with complications, 3 epididymitis, 3 arthritis, and 1 iritis. In 2 cases of epididymitis, all the laboratories gave negative reports.

Of the 141 cases, there were 128 tests reported by each serologist. Fifty-one, or 39.9 per cent, agreed, and 77, or 60.1 per cent, disagreed.

Warden (1915) maintains that, with regard to the complement-fixation test, the fat products in a gonococcal autolysate are as important antigenically as the nitrogenous part. He found that the fatty portion suspended in alcohol possessed a much higher antigenic power than the watery antigen of commerce. With his lipoid antigen he got more positive tests, and moreover the positive reaction appeared earlier in the disease, and endured longer. In a further paper (1916) he again reiterates the superiority, as an antigen, of an alcoholic solution of the fatty moiety of the gonococcus over watery extracts.

Pearce (1915) states that two principal types of gonococci can be recognised by agglutination and by the complement-fixation test. These two species correspond to the adult and infant types of infection as seen clinically. Three strains isolated from cases of ophthalmia were found to belong to the adult type. He urges that a polyvalent antigen as used for the blood test should contain a strain of the infant type in addition to the strains of the adult variety.

Thomas, Ivy, and Birdsall (1915) published, as a continuation of their previous paper in 1914, a series of results obtained in 216 cases of gonorrhœa by employing antigens of the following types of organisms, each antigen containing several strains.

¹ It would be much more easy to explain the positive reaction with catarrhalis antigen by assuming that the patient had a *Micrococcus catarrhalis* infection of the nasal and bronchial passages as well as gonorrhœa.
—AUTHOR.

	No. of Cases.	Positive.	Negative.
(1) Six strains of <i>Micrococcus albus</i>	216	0	216
(2) Six strains of the pneumococcus	216	4	212
(3) Six strains of streptococci	216	1	215
(4) Six strains of <i>Micrococcus aureus</i>	216	3	213
(5) Three strains of <i>Micrococcus catarrhalis</i>	180	5	175
(6) Six strains of "corynebacterium" pseudo-diphtheriticum	160	1	159
(7) Six strains of <i>B. coli</i>	160	0	160
(8) Nine strains of gonococci	216	67	149
(9) Parke Davis & Co. gonococcal antigen	216	67	149
(10) Fifteen strains of meningococci	216	1	215

The antigens in all cases were prepared by washing off a forty-eight hours' growth of the organism with sterile distilled water. The emulsion was shaken for one hour and then allowed to autolyse for twenty-four hours at 37° C. Finally it was heated in a water bath for one hour at 60° C. The technique of the complement-fixation test was the same as employed for the Wassermann reaction. They found that the antigens were as good at the end of the investigation as at the beginning, so that they did not show any apparent deterioration. Some sera gave positive reactions with gonococcal antigens only, a few gave positive reactions only with non-gonococcal antigens, and some gave positive results with both gonococcal antigen and the antigen of some other type of organism. They maintain that this is explained by the fact that frequently mixed infections occur in gonorrhœa, and in some cases after the gonococcus has ceased to be viable the inflammation is continued by the superimposed secondary germs.

Ribes and Lawrence (1915) were able to diagnose a case of gonorrhœal iritis, resulting from an old latent gonorrhœa, by means of the complement-fixation test. This case was treated successfully with gonococcal vaccine.

Over (1915) published the results obtained in 375 cases, in 218 of which a gonorrhœal infection was present or suspected.

	Number.	Positive.	Negative.
(1) Acute urethritis, ten days' duration or less, and with gonococci in the smears	21	0	21
(2) Acute urethritis, three to six weeks' duration	17	9	8
(3) Chronic urethritis of over six weeks' duration	22	13	9
(4) Epididymitis :			
(a) Definite history of gonorrhœa	19	15	4
(b) No history of gonorrhœa	4	0	4
(5) Prostatovesiculitis (majority chronic)	40	22	18
(6) Arthritis, acute :			
(a) No history of gonorrhœa	10	0	10
(b) History of recent gonorrhœa	8	8	0
Arthritis, chronic :			
(c) Clinically gonorrhœal	8	6	2
(d) No definite history	11	3	8
(7) Folliculitis	7	0	7
(8) Stricture (no gonorrhœa for ten years)	3	0	3
(9) Conjunctivitis, acute (gonococci found)	1	1	0
(10) Salpingitis	23	14	9
Of the 9 negative cases, 4 were found at operation to be tuberculous.			
(11) Cases in which gonococcal vaccine had been administered	8	8	0

Tests were also performed on 130 sera, using both a monovalent and a hexavalent antigen; the latter was found on the whole to give distinctly better results. With it

4 cases were positive which gave negative reactions with the monovalent antigen. In those sera in which both antigens gave positive results, the hexavalent gave, almost without exception, the stronger reaction. He concludes by saying that the most strongly positive results are obtained in cases in which the gonorrhœal lesions occupy sites in which there is possibly a lack of free drainage.

Davidson (1915) contributed an article entitled "Gonorrhœa Complement-fixation Test as Aid in Diagnosis," and Williams (1915) also wrote a paper, "Diagnosis of Gonococcal Affections by Complement-fixation Test." The writer has not been able to gain access to their works.

Irons and Nicoll (1915) used an anti-human rabbit hæmolytic system and polyvalent gonococcal antigen prepared by themselves, as well as the commercial antigen on the market. Both gave consistent results. The maximum antigenic dose used was one-quarter to one-third of the anti-complementary dose.

They give the following results :—

	No. of Cases.	Positive.	Negative.
(1) Metastatic gonococcal infections (chiefly arthritis, iritis, or sepsis)	14	13	1
(2) Vulvo-vaginitis in children (duration two to many months)—			
(a) Gonococci isolated by culture	12	7	5
(b) Gonococci not isolated	5	1	1

They found that the complement-fixation reactions varied from week to week, indicating that there are rapid fluctuations in the immunity of the patients. They conclude as follows :—

(1) A strong or moderately positive reaction obtained with adequate controls indicates the presence or recent existence of gonorrhœa.

(2) A weakly positive reaction has only a limited confirmatory value, and the test should be repeated for diagnosis.

(3) The reaction may fluctuate from positive to negative and *vice versa* during the course of the infection. This must be taken into account when a negative result is obtained in a suspected case.

(4) The reaction may fluctuate to negative when gonococci are still present in the body, and so one should only interpret a single negative test with great caution, either in the diagnosis of infection or in the determination of cure.

Shupe (1916), in a series of 1000 complement-deviation tests, states that no case was found in which the result was positive when the patient had not been infected with the gonococcus, or did not have gonococcal vaccine. He found that in acute cases of gonorrhœa, when it is generally very easy to demonstrate the gonococcus microscopically, the test is generally negative in the first five weeks, and becomes positive from the fifth to the sixth week in uncomplicated cases. If the infection remains limited to the anterior urethra and subsides by the seventh or eighth week, the patient may never give a positive reaction. A positive reaction occurring in a person clinically cured of gonorrhœa indicates the presence of a gonococcus focus, and these persons are potentially capable of infecting others. The antibodies may remain for five or six weeks after all organisms have disappeared, and a negative test following a positive one in a supposedly cured case is good evidence that the patient is cured. About 30 per cent of the cases in this series were still positive when supposed to be cured. He considers that the test is of particular value in gonorrhœal arthritis, since in this class about 100 per cent of positive reactions are obtainable. One hundred per cent of positive results were also obtained in cases of acute epididymitis after five weeks from the onset of the disease. Cases with chronic prostatitis, seminal vesiculitis, and posterior urethritis gave 80 per cent positive reactions. An uncomplicated stricture does not give a positive result. He points out that an individual

may have two or more infections, and in interpreting a positive test it should be borne in mind that gonorrhœa is a very widespread disease.

Priestley (1919) got good results with the complement-fixation test in gonorrhœa, by using a gonococcus antigen prepared from twenty-four to forty-eight-hour cultures. The gonococci were dried over a water bath, ground up with powdered glass, extracted with ether, dried again, and stored in the ice chest. To prepare the stock antigen an amount equal to 100 mg. of the original dried suspension is weighed and suspended in 10 c.c. saline.

Bowman and Saylor (1918) did complement-fixation tests in 383 cases of gonorrhœa with little discharge and in whom no gonococci could be found. Of these 177 were positive. Seventy-seven patients gave a definite history of having had gonorrhœa, and 60 of these were positive and 17 negative. Of 36 cases diagnosed as epididymitis, 19 were positive and 17 negative. Of 20 cases diagnosed as prostatitis, 14 were positive and 6 negative. In 21 cases of orchitis, 15 were positive and 6 negative. In 4 cases of chronic gleet, 3 were positive and 1 was negative. Three cases diagnosed as rheumatic fever were positive. Of 26 cases with a clinical diagnosis of myalgia and no clinical evidence of gonorrhœa, 8 were positive and 18 negative. The test was never positive in localised anterior urethritis, nor was it usually positive before the sixth week of the disease if no complications were present. They state that a patient should not be considered cured if the test is still positive even two months after the disappearance of all clinical symptoms.

Dixon and Priestley (1919) carried out 840 complement-fixation tests on 625 cases of gonorrhœa. They found that those cases which did best showed an early strong positive and a subsequent fall while in hospital. The technique employed was that described by Priestley (1919). They state that in diagnosis a positive result is strongly indicative of active gonococcal infection. A single negative is of no value, but a second negative in two or three weeks is strong presumptive evidence of absence of infection. Cases doing well show a positive reaction by the ninth or tenth week, which soon begins to fall, such fall coinciding with clinical improvement. Cases in which a strong positive reaction is maintained over several weeks still have an active focus. The administration of detoxicated gonococcal vaccine in doses of 1000 millions or more produces an artificial power of fixing the complement, but they do not consider that this runs *pari passu* with immunity. They consider that the complement-fixation test should prove of the greatest value in the diagnosis of obscure pelvic diseases in women, so often the result of gonorrhœa.

Magner (1920) used the author's technique and antigen (see next chapter) in a series of 200 cases, comprising 110 cases of gonorrhœa and 90 controls. The following are his conclusions:—

(1) The complement-fixation reaction will prove of real value both in the diagnosis of gonorrhœal infections and in the determination of the period of infectivity.

(2) It is probable that with more accurate information as to the serological types of the gonococcus a more sensitive antigen will be available and more specific results obtained.

(3) Negative results are common during the first ten or twelve days of the discharge. After this period the great majority of cases react positively. Positive results, however, may be obtained as early as the fourth day.

(4) A certain number of mild cases in which the infection appeared to be limited to the anterior urethra reacted negatively through the attack.

(5) The more extensive the inflammation the greater the probability of a positive result. Cases showing systemic complications invariably give such a result.

(6) The complement-fixing antibody persists in the serum for about three months after the destruction of the organism, during which period the reaction remains positive.

(7) The administration of an ordinary autogenous gonococcal vaccine during the course of treatment does not lead to a greater persistence of antibodies, the serum becoming negative in about the same period after the final injection.

(8) The criterion of cure and non-infectivity is therefore a change in the reaction from positive to negative three months after disappearance of all symptoms and cessation of all treatment.

Smith and Wilson (1920) compared the diagnostic results obtained by smears, cultures, and the complement-fixation test in cases of chronic gonorrhœa in women. They concluded that the latter test was of undoubted value.

Kilduffe (1921) states that the complement-fixation test becomes positive about six weeks after the onset of gonorrhœal urethritis. In acute exacerbations of chronic gonorrhœa the test was positive in 80 per cent. In cases of prostatitis 30 to 40 per cent of the reactions were positive; in pyosalpinx 60 per cent and in arthritis 80 to 100 per cent were positive. He states that positive results are of greater diagnostic value than negative results.

Lailey and Cruickshank (1921) were not particularly satisfied with the value of the test. In 217 cases of gonorrhœa in women, 116 gave positive reactions and 96 were negative. The cases with negative reactions covered all stages of the infection from recent cases to chronic conditions of years' duration.

Cook and Stafford (1921) were unable to classify different strains of gonococci by the complement-fixation test, or by agglutination reactions, or by means of the method of absorption of agglutinins.

Osmond, T. E. (1922), used the author's technique and antigen (see next chapter) in a series of 1000 tests. This series comprised 300 men and 700 women. As a result of his investigations he considers that the value of this test in diagnosis is at least as great as that of the Wassermann reaction in syphilis. In his experience the reaction becomes positive earlier in the disease than does the Wassermann in syphilis. In the average clinic the percentage of all cases of clinical gonorrhœa in women in which gonococci can be demonstrated is very small, and it is in the diagnosis of these female cases in which the test is so valuable.

The most striking points regarding the test are :—

- (1) The early stage at which a positive result may be obtained.
- (2) The relatively high percentage of positives in undoubted cases of active gonorrhœa (average 86.5 per cent).
- (3) The low incidence of "false positives"—only 3 in 1000. In none of these cases could gonorrhœa be absolutely excluded, and the cases were only included in category (4) because the medical officers in charge of the cases marked them "non-venereal."
- (4) A "doubtful" test is at least suspicious, and should be repeated. It should also stimulate a further careful examination.

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CHAPTER XXIX

THE AUTHOR'S RESEARCHES ON THE COMPLEMENT-FIXATION TEST IN GONORRHŒA

EARLY in 1918 the author commenced to carry out a research on the complement-fixation test in gonorrhœa. On the advice of Col. L. W. Harrison he employed the long method of fixation introduced by Dr. Griffiths, wherein the mixture of the serum to be tested, antigen and complement, is allowed to remain all night in the ice chest before the sensitised sheep's corpuscles are added. Undoubtedly by this method much more delicate results are obtained than by the shorter process where the antigen, serum, and complement are placed in the water bath at 37.5°C . for only half an hour before addition of the sensitised corpuscles.

The author first used an ordinary saline emulsion of gonococci as the gonococcal antigen, and found that by the ice-chest method the anti-complementary action of this antigen was as follows :—

<i>Strength of Antigen.</i>			<i>Amount of Complement deviated.</i>	
50 million gonococci per c.c.			Absorbed less than one M.H.D.	
100	"	"	"	one M.H.D.
250	"	"	"	two M.H.D.
500	"	"	"	four M.H.D.

It was obvious, therefore, that with this antigen the proper strength to use was an emulsion containing from 50 to 100 million gonococci per c.c.

Experiments were next carried out in order to ascertain what dilution of a known positive serum would give the strongest results in the test. Dilutions varying from $\frac{1}{10}$ to $\frac{1}{100}$ were employed, and it was noted that the $\frac{1}{10}$ to $\frac{1}{20}$ dilutions gave stronger reactions than when the higher dilutions were used. Still later it was found that sera used in a dilution of $\frac{1}{10}$ gave more distinct results than when the dilution was $\frac{1}{20}$. It was decided, therefore, to use in the routine test an antigen containing 100 million gonococci per c.c. in suspension, and to dilute the serum to be tested 1 in 10.

The long-fixation ice-chest method was employed, and quite satisfactory results were obtained.

New Method of preparing the Gonococcal Antigen.—About this time the author discovered that gonococci were easily soluble in $\text{N}/10$ sodium hydroxide, and it seemed possible that such a solution might act as a good antigen provided it was brought to a neutral reaction.

When acid is added to an alkaline solution of gonococci, the germ substance is precipitated when the fluid becomes slightly acid. In preparing the antigen, therefore, acid was added just short of precipitation, so that the solution remained nearly neutral, or slightly on the alkaline side of neutrality. It was found by experiment that an antigen prepared in this way was much less anti-complementary than a gonococcal emulsion of the same strength. Thus a faintly alkaline solution of gonococci of a strength

equal to 200 million germs per c.c. was no more anti-complementary than an emulsion of non-autolysed cocci at a strength of 50 million germs per c.c. In other words, the germ solution could be used in a concentration four times greater than the germ suspension.

Moreover, it was further superior to the emulsion in antigenic power, since in the actual tests on gonococcal sera the reactions were more markedly positive with the solution than with the suspension of germs. Finally, the solution antigen was tested against the material supplied by Parke Davis & Co. The latter is prepared by filtering an emulsion of autolysed gonococci through a Berkefeld filter, the filtrate being used as the antigen. The author's new antigen was found to be superior to the Parke Davis product, since the latter was more anti-complementary and less powerful antigenically. Having ascertained these facts, it was decided that a neutral solution of gonococci was the best antigen to use in the complement-fixation test for gonorrhœa. The results obtained have amply proved its superior value.

Method of Standardising the New Antigen.—Solutions of gonococci are very easy to prepare and very easy to standardise. All that is necessary is a standard emulsion containing 1000 million gonococci per c.c.

This is primarily prepared by counting the number of cocci in a given concentrated emulsion by Wright's method and then diluting to the required strength, viz. 1000 millions. This standard will keep good for many months, provided the emulsion is slightly acid in order to prevent the cocci from autolysing.

To make a standard antigen, a few cultures of gonococci are washed off into a test tube with a little sterile saline. This concentrated emulsion is thoroughly shaken up with small glass beads to break down any clumps.

A tube of the same diameter as the standard is taken, and one cubic centimetre of the concentrated saline emulsion of gonococci is added to it. Normal saline is now added until the opacity exactly matches that of the standard 1000 millions per c.c. The total bulk is now estimated. Suppose, for example, it is found to be 40 c.c. This shows that the 1 c.c. of the concentrated emulsion has been diluted forty times, and that it contained 40,000 million germs. The strength of the concentrated emulsion is therefore 40,000 millions per c.c.

Take now 1 c.c. of the original concentrated emulsion; add to this five drops of normal alkali (NaOH), shake, and allow to stand in the incubator at 37.5° C. over night. In the morning the gonococci will be found to have dissolved into a clear solution. Three drops of normal acid should be added to bring the reaction to a little on the alkaline side of neutrality. Add 19 c.c. of normal saline containing 0.5 per cent carbolic acid, and we now have practically a neutral solution of gonococci of a strength of 2000 millions per c.c. Such a solution makes a good stock antigen. The carbolic acid is added to prevent the development of germs. This is very necessary, since the presence of organisms would render the antigen very anti-complementary.

Before use it is necessary to dilute the stock antigen 1 in 10 with normal saline. This preliminary dilution brings it to a suitable strength for the test, viz. 200 millions per c.c. It further dilutes the carbolic acid to 0.05 per cent. This is necessary, since 0.5 per cent carbolic prevents the proper action of the complement in the test.

The diluted antigen corresponding to a strength of 200 million gonococci per c.c. deviates as a rule $\frac{1}{4}$ to $\frac{1}{2}$ of one minimum hæmolytic dose of complement. Thus, if the titration of the complement with saline gives the M.H.D. as $\frac{1}{60}$, the titration with the antigen usually gives the M.H.D. as $\frac{1}{50}$.

Keeping Power and Stability of the Stock Antigen.—The author has used stock antigen which was made up nearly two years ago, and it was found to give quite satisfactory results in the test. This is sufficient to show that it is quite stable. The stock bottle was as a rule kept in the ice chest in the dark, but on several occasions it was left at room temperature, exposed to the light. It is not known whether exposure

to light has any deteriorating effect upon it, but moderate temperatures do not damage it to any appreciable extent. It can stand boiling for five minutes and still retain much of its original power. Boiling for thirty minutes, however, caused a considerable drop in its antigenic value. An antigen which had been heated to 80° C. for three hours had deteriorated about $\frac{1}{3}$, so that a triple positive (+ + +) reaction obtained with the unheated antigen was only double positive (+ +) with the same antigen heated to 80° C. for three hours, or to boiling-point for half an hour.

These facts are rather important, as they tend to prove that vaccines should retain their antigenic properties for one or two years, provided they are kept cool and in the dark. They indicate also that it is bad to heat vaccines for any length of time to a temperature of about 80° C. and upwards. Heating to 60° C. for one hour (as is often carried out in the sterilisation of vaccines) is not likely to do much harm to the specific antigenic properties of the vaccine.

Is a Compound Antigen composed of many Strains better than a Single Strain Antigen?—Many observers have maintained that the gonococcus belongs to a group of organisms consisting of many closely allied yet slightly different strains.

This has been proved with regard to the meningococcus, since at least four types of the latter organism have been isolated and identified by the agglutination test.

The writer attempted to find out if there were different types or strains of gonococci, by means of the complement-fixation test. Fifteen strains of the germ were isolated in pure culture from fifteen different patients; some of these strains were cultivated from gonococcal joints and others from epididymitis cases. A single antigen was made up from each different strain isolated, and finally a compound antigen was made up from equal parts of the fifteen different antigens compounded together.

The sera of 50 cases of gonorrhœa were then tested out with each of the single antigens as well as with the compound antigen. In addition a meningococcal antigen composed of the four different types of meningococci was employed, and also an antigen composed of one type only.

This investigation therefore required a total of eighteen times fifty, or 900 blood tests. The results obtained are shown in the following table:—

Antigen employed.	No. of Sera tested.	Strength of Reaction (Percentage Results).				
		+++	-	++-	---	--
		Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Gonococcus, strain 1	50	72	6	9	0	13
" " 2	"	56	8	14	2	20
" " 3	"	55	8	19	0	18
" " 4	"	54	10	18	0	18
" " 5	"	52	9	14	0	25
" " 6	"	50	10	29	0	11
" " 7	"	45	3	27	0	25
" " 8	"	44	10	20	2	24
" " 9	"	42	8	17	0	33
" " 10	"	42	0	17	8	33
" " 11	"	38	10	24	2	26
" " 12	"	34	10	30	2	24
" " 13	"	33	8	8	0	51
" " 14	"	32	13	42	0	13
" " 15	"	17	8	33	0	42
Compound gonococcus antigen (strains 1-15)	"	51	3	23	3	20
Meningococcus (single strain)	"	10	0	41	10	39
Compound meningococcus (types 1-4)	"	45	0	25	5	25

It should be noted that the fifty gonococcal sera employed were the same in all cases. If we take the above Table and simplify it by taking the first three columns as positive results and the last two as negative, we get the following percentages :—

Gonococcus antigen, strain 1 = 87% positive and 13% negative.				
"	"	2 = 78	"	22
"	"	3 = 82	"	18
"	"	4 = 82	"	18
"	"	5 = 75	"	25
"	"	6 = 89	"	11
"	"	7 = 75	"	25
"	"	8 = 74	"	26
"	"	9 = 67	"	33
"	"	10 = 59	"	41
"	"	11 = 72	"	28
"	"	12 = 74	"	26
"	"	13 = 49	"	51
"	"	14 = 87	"	13
"	"	15 = 58	"	42
Compound gonococcus antigen = 77		(strains 1 = 15)	"	23
Meningococcus antigen = 51		(single strain)	"	49
Compound M. antigen (types 1-4) = 70			"	30

If we now take the total average of the fifteen single gonococcal antigens we get the following comparative Table :—

Antigen.	Positive Results.	Negative Results.
Single gonococcal strains	74	26
Compound gonococcal antigen	77	23
Single meningococcus strain	51	49
Compound meningococcus antigen	70	30

It is apparent, therefore, that the compound antigens are better than the average single strain antigens. If, however, we again examine the results obtained by the single gonococcal antigens we find that strains 1, 2, 3, 4, 6 and 14, when used alone, gave a higher percentage of positive reactions than were obtained from the compound antigen, while the remaining nine strains gave a lower percentage.

The best single strain antigen (No. 6) gave 89 per cent positive reactions, while the poorest (No. 13) gave only 49 per cent. It would seem from this that some strains of gonococci are very poor antigenically, whilst others are apparently powerful key strains, which are antigenic towards all the other varieties. A key strain such as No. 6 proved to be better than even the compound antigen composed of many varieties. This weakness in the compound antigen was no doubt due to the fact that it contained certain feeble strains in its composition. Theoretically, therefore, the best antigen would be one compounded of strongly antigenic types of gonococci, such as strains 1, 2, 3, 4, 6 and 14.

It is interesting to note that antigens prepared from meningococci were able to give positive reactions with gonococcal sera, but these reactions were not usually so strong as those obtained with gonococcal antigens.

A number of tests were also carried out with the sera of patients, taken during or soon after an attack of cerebro-spinal meningitis. It was proved thereby that a

gonococcus antigen could give strongly positive reactions with a meningococcal serum. In this respect indeed the gonococcal antigen gave as many positive results as the meningococcus antigen.

We may summarise the results of the above research as follows :—

(1) A definitely negative serum was negative with antigens prepared from any given strain of gonococcus.

(2) A strongly positive serum was definitely positive with an antigen of any given type.

(3) A weakly positive serum gave varying reactions with different strains of antigen. With strongly antigenic strains, the results were definitely positive. Other strains gave feeble positives, whilst the weakest antigenic strains often gave a completely negative reaction.

(4) A strongly positive gonococcal serum often gave only a weakly positive reaction with a meningococcus antigen, and a feebly positive gonococcal serum usually gave a negative result with the meningococcus antigen.

(5) With regard to meningococcal sera, a gonococcus antigen usually gave results as definitely positive as those obtained with an antigen prepared from meningococci. It would appear, therefore, that the gonococcus is the parent strain of the meningococcus.

(6) The author was unable to separate out definite types of gonococci by means of the results obtained in the above complement-fixation reactions. Four definite types of meningococci have been established by the agglutination test, and Bell (1918) claims to have identified these types also by means of the complement-fixation test, carried out with meningococcus antigens prepared by the author's method.

The writer was somewhat sceptical with regard to this claim, so six cultures of gonococci and six cultures of meningococci containing types 1-4 were prepared. These twelve cultures were sent to Major Bell and, without allowing him to see the key to the numbers, he was asked to prepare antigens from each, and find out thereby which were gonococci and which were meningococci. He was also asked to ascertain to which types the meningococci belonged. The results he sent back were all correct save one.

Differences in Antigenic Power due to Mode of Preparation.—The writer was fortunate enough to discover a fallacy in his experiments with regard to the varying antigenic power of different strains of gonococci.

With the first thirty out of the fifty gonococcal sera tested, strain eleven proved to be the weakest of all the antigens, since it gave the lowest percentage of positive reactions. At this stage the bottle containing strain eleven was broken. Another supply of this antigen was prepared from fresh subcultures of the organism, which fortunately had been kept alive.

The second bottle of antigen made from this strain, instead of being the weakest, was found to be one of the strongest antigens with the remaining twenty sera tested, so that the average percentage of positive reactions was raised from 56 per cent to 72 per cent. This is sufficient to show that the potency of an antigen prepared from any given strain depends to a large extent on the way in which that antigen is prepared.

So far as could be ascertained, the efficiency of the prepared antigen depended upon four factors: (1) Concentration; (2) Thoroughness of solution; (3) Reaction; (4) Saline content.

An antigen with a large number of gonococci per c.c., thoroughly dissolved, was likely to be more potent than one in which the germs were fewer in number and where the solution was not so complete.

With regard to the third factor, viz. reaction, several experiments were carried out in order to determine this point. Theoretically the antigen solution ought to be exactly neutral.

If the solution is rendered slightly acid the gonococcal substance begins to precipitate, and this tends to make the antigen more anti-complementary, and so it cannot be used in high concentrations in the test.

On the other hand, if the antigen is too alkaline the latter is liable to affect the action of the complement in the test. A series of complement-titrations were carried out with varying strengths of acid and alkali, and it was found that the complement was not so potent when the reactions of the fluids were as low as even N/1000 acid or alkali.

This is to say +1 acid or alkali (Eyre's scale) is sufficient to injure the action of the complement in the blood test.

One-tenth of this reaction, however, viz. N/10,000 acid or alkali, had no injurious effect whatsoever.

The stock antigen, therefore, should not be more than +1 acid or +1 alkaline. Factor four, viz. the saline concentration, is also of some importance. High concentrations of saline are anti-complementary, partly because they tend to precipitate the antigen, and partly because they tend to precipitate the colloid proteins in the serum itself. Suppose we were to prepare gonococcal antigen by dissolving the germ in 10 per cent NaOH, and then to bring to nearly the neutral point with 10 per cent HCl, the result would be that the antigen contained about 10 per cent NaCl.

Normal saline, which is used as the diluting fluid in complement-fixation tests, is 0.85 per cent NaCl.

If the salt content of the antigen was so high that in the test proper the percentage of NaCl amounted to 2.5 per cent, then practically all the reactions would come out positive. Since, however, the stock antigen is diluted ten times with normal saline before use, the amount of salt in this dilution is not likely to have an adverse effect on the test itself. Nevertheless the stock antigen should not contain a saline concentration much over 0.85 per cent NaCl. For this reason it is necessary to dissolve the germs in a minimum of alkali. About five drops of N.NaOH to each c.c. of the original concentrated emulsion of gonococci is sufficient for this purpose.

Comparison of Antigens prepared from different Strains of Gonococci.—From the above researches it is obvious that if we wish to compare accurately the antigenic power of different strains of gonococci, then it is necessary to make up the various antigens in exactly the same manner, so that the state of solution, concentration, reaction and saline content are all the same. Unfortunately these factors were not ascertained definitely in the author's first experiments, and for this reason the value of the comparative results obtained is not so great as it should have been.

To ascertain definitely whether different strains of gonococci vary in antigenic value or not, the writer's series of 50 tests with 19 antigens would require to be repeated.

Van Saun (1912) showed that the antigenic properties of the gonococcus varied according to the culture medium on which it was grown. For proper comparative results, therefore, each strain would require to be cultivated upon the same kind of culture medium, and each antigen would require to be made up in identically the same manner, so that the concentration, state of solution, reaction and saline content were the same in all.

Author's Method of carrying out the Complement-Fixation Test for Gonorrhœa.—Careful preparation of the reagents is essential for the best results.

(1) "**Complement.**"—A guinea-pig is bled about twelve hours before the tests by cutting the carotid arteries. The blood is allowed to clot, put on ice, and immediately before use the serum is separated from the clot. It is cleared by centrifuging, if any red cells are present.

(2) "**Amboceptor.**"—Four or five injections of from 2 to 5 c.c. of a 50 per cent solution of fresh sheep's red blood cells in normal saline (0.85 per cent) are made into the ear vein of a rabbit, or into the peritoneal cavity at intervals of five days. Ten days after the last injection the serum is titrated to determine its value as an amboceptor. If suitable, the rabbit is bled, the blood being allowed to clot, the serum withdrawn, then

inactivated by heating at 56° C. for thirty minutes to destroy its natural complement. It is then placed in ampoules and stored on ice.

(3) **"Red Blood Cells."**—Fresh sheep's blood cells are washed with saline and centrifuged several times (usually four) until the supernatant fluid is quite clear.

(4) **"Antigen."**—The preparation of the new gonococcal stock antigen has already been fully described.

(5) **Preliminary Titration of the Amboceptor** (Col. Harrison's method).—To ascertain the minimum amount of rabbit's anti-sheep-cell serum which is sufficient to hæmolyse completely one volume of sheep cells with the help of an excess of complement, a number of test tubes are set out in a row, and into each is placed one volume of a 3 per cent suspension of the washed sheep cell deposit. A series of dilutions of the anti-sheep serum is prepared—*e.g.*, 1 in 125, 250, 500, 750, 1000, 1500, 2000, and from each of these dilutions in turn a volume is taken and added to the sheep cells in one of the tubes, so that the row of tubes now contains a series of equal quantities of sheep cells in contact with varying amounts of hæmolytic amboceptor. After half an hour one volume of a 1 in 10 dilution of fresh guinea-pig serum (containing complement) is added to each of the tubes. A volume of saline is placed in each tube to make the bulk of fluid equal to that in the test itself. It is important in all titrations preliminary to the test that the bulk of fluid in each tube should be the same as it is in the test itself, since concentration affects the titre. In the author's technique four volumes are used in the test proper—one each of serum, complement, extract and cells. All the tubes are placed in the incubator at 37° C. The tubes are shaken about every ten minutes, and the reading is taken at the end of an hour. The tube is sought which contains the smallest amount of amboceptor, and in which there is complete hæmolysis.

The dilution of amboceptor serum in this tube represents the minimum hæmolytic dose (M.H.D.) of the titrated amboceptor. An amboceptor of lower titre than 1 in 1000 should not be used, since a low-titre amboceptor serum has to be added in such large amounts to the cells that agglutination of the latter is apt to occur. Another objection to the use of low-titre amboceptor is that, other things being equal, the titre of complement against cells sensitised with such an amboceptor is lower than when the cells are sensitised with a powerful amboceptor. This affects the test, since, as Browning points out, hæmolytic activity and deviability of a complement do not run *pari passu*. An excess of complement is used, since one M.H.D. of amboceptor will not effect complete hæmolysis when working with one M.H.D. of complement, and, within limits, the larger the amount of amboceptor with which the cells are sensitised, the smaller the M.H.D. of complement. This is mentioned here as it affects the question of the amount of amboceptor to use in sensitising the cells for the titration of complement and for the test itself.

(6) **Preparation of the Sensitised Sheep Cells.**—For sensitising the cells some workers use 2½, others 4 M.H.D., and still others larger quantities of amboceptor. Whatever quantity is to be used in the test proper must be used in titrating the complement. Since in the test proper the cells come into contact with a small but variable amount of hæmolytic amboceptor which is present in the human serum, Harrison always considered it better to sensitise the cells beforehand with a large amount of amboceptor, so that in the test proper the M.H.D. of the complement, as ascertained by previous titration, will not be affected by the additional amboceptor in the tested sera. For this reason he sensitises the sheep cells with not less than 5 M.H.D. of hæmolytic amboceptor.

To make up the sensitised cells for titration of complement and for the test, assuming that 20 c.c. of sensitised cells are required, and that the M.H.D. of amboceptor is 1 in 1500, 10 c.c. of a 1 in 150 dilution of the amboceptor is prepared and added to an equal quantity of a 6 per cent suspension of sheep cells, making 20 c.c. of a 3 per cent suspension of cells in a 1 in 300 dilution of amboceptor. A sufficient quantity of sensitised cells should be prepared to suffice for all preliminary titrations, and for all the tests carried

out on any one day. There is a possibility of error if one batch is sensitised for titrations, and another for the tests. It is well to allow the cells to remain in contact with the amboceptor for half an hour before using them.

Amboceptor is very stable, and need not be titrated more often than once in about three months.

(7) **Standardisation of the Complement.**—The complement should be titrated against the stock antigen diluted 1 in 10 with 0.85 per cent saline as used in the test. To twelve Wassermann tubes add 0.1 c.c. of guinea-pig's serum (complement) diluted as follows :

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
$\frac{1}{10}$	$\frac{2}{10}$	$\frac{3}{10}$	$\frac{4}{10}$	$\frac{5}{10}$	$\frac{6}{10}$	$\frac{7}{10}$	$\frac{8}{10}$	$\frac{9}{10}$	$\frac{10}{10}$	$\frac{11}{10}$	$\frac{12}{10}$

To each add 0.1 c.c. of the diluted antigen (1 in 10) and 0.1 c.c. of saline. Shake the tubes and place the tray in the ice-chest for one hour. Then put the tray in a water bath at 37° C. for half an hour. Add to each tube 0.1 c.c. of fully sensitised sheep's corpuscles (3 per cent suspension). Replace the tray in the water bath at 37° C., and take the readings after fifteen minutes. The lowest dilution of complement which produces hæmolytic dose in the tubes should be taken as one minimum hæmolytic dose with certain reservations which are explained below.

(8) **Inactivation of the Serum.**—The serum to be tested is inactivated by heating to 55° C. for ten minutes in a water bath before dilution.

(9) **The Technique employed in carrying out the Actual Test.**—For each test four tubes, A, B, C and D, are employed.

(a) To A, B, C and D, add 0.1 c.c. of the inactivated serum (diluted 1 in 5).

(b) To A add complement 0.1 c.c. containing $3\frac{1}{2}$ minimum hæmolytic doses.

„ B „ „ „ 3 „ „

„ C „ „ „ $2\frac{1}{2}$ „ „

„ D „ „ „ $2\frac{1}{2}$ „ „

(c) To A, B and C add 0.1 c.c. compound antigen (diluted 1 in 10). Tube D acts as the control, and to it is added 0.1 c.c. of saline instead of antigen.

(d) Place the tubes in the ice-chest overnight, and next morning add to each 0.1 c.c. of a 3 per cent emulsion of fully sensitised corpuscles. Then place the tubes in the water bath at 37° C., and take the reading after fifteen minutes (with reservations, see below). The control tube D should show complete hæmolytic dose.

Hæmolytic dose in A, B and C indicates a negative reaction. No hæmolytic dose in A, B and C indicates a strong positive.

No hæmolytic dose in A alone indicates a weak positive.

An antigen control, containing no serum but an equivalent amount of saline and $2\frac{1}{2}$ M.H.D., is necessary, since the antigen absorbs a considerable amount of complement during the long period of fixation in the ice-chest. It is not practicable to use the long fixation method in the process of standardising the complement, since the complement deteriorates from day to day. Known positive and negative sera should always be included in the series, and all the tests should be rejected in the event of these controls being unsatisfactory.

Important Note with reference to the "Reservations" made above.—It will be observed that the preliminary titration of the complement only gives the worker a rough idea of the strength which will be required to cover the anti-complementary power of the antigen. In the preliminary titration the complement is exposed to the antigen for one hour in the ice-chest and for half an hour at 37° C. In the actual test, however, the complement is exposed to the antigen for some twelve to fifteen hours in the ice-chest. If in the preliminary short titration against antigen it is found that the minimum hæmolytic dose of complement is $\frac{1}{10}$ we cannot argue from this that such is the M.H.D. when the exposure has been all night in the ice-chest. The author's experience has shown that the M.H.D. in the latter case is always lower, and in some

cases it will be found that the antigen control tube in the test may not hæmolyse with its $2\frac{1}{2}$ M.H.D., showing that either the complement has deteriorated during the night's exposure in the ice-chest, or else that more complement has been fixed by the antigen on account of this longer exposure.

It is not an unfrequent occurrence, therefore, in the carrying out of these tests, that we find a shortage of complement next day when the sensitised cells are added, so that none of the controls go, and the whole batch of tests is a failure.

In order to avoid these failures the author always allows for the weakening of the M.H.D. of the complement which occurs in the overnight fixation method. In actual practice one should read the strength of the complement in the short preliminary titration in fifteen minutes, and take a lower dilution as the M.H.D. in the following manner.

If the reading shows complete hæmolysis with dilutions of complement at $\frac{1}{70}$, then take the M.H.D. at two points lower, viz. $\frac{1}{50}$.

When complete hæmolysis occurs at a dilution of $\frac{1}{40}$ to $\frac{1}{60}$ then only come down one point, so that $\frac{1}{60}$ would become $\frac{1}{50}$, $\frac{1}{50}$ would become $\frac{1}{40}$, and $\frac{1}{40}$ would become $\frac{1}{30}$.

When, however, complete hæmolysis only occurs in dilutions of $\frac{1}{20}$ to $\frac{1}{30}$, then actual experience has shown that the M.H.D. should not be taken as lower.

It is difficult to give any real explanation for these practical points, unless it is a fact that when the M.H.D. is a high dilution then a bigger deterioration takes place during the night than in the case where the M.H.D. is a low dilution.

There is a further reservation with regard to the reading of the actual test, viz. that no definite rule of thumb time can be laid down for the reading of the results.

It has already been pointed out that the exact margins of complement cannot be accurately gauged, because the length of time employed for the actual test is much longer than that which must necessarily be used for the preliminary titration of the complement.

Since these exact margins are not definitely known, it is unreasonable to read the results of the actual test in any given stated time. It seems much more sensible to read the results so soon as all the controls have gone.

Thus in practice the author takes the readings sometimes in five, sometimes in ten, and sometimes in fifteen minutes and longer, depending entirely upon how long it takes for complete hæmolysis to occur in the serum control, the antigen control, and in the known negative control.

Some workers have tried the complement-fixation test for gonorrhœa, and maintain that the results are very poor. This opinion undoubtedly arises partly from the fact that the results are read in a rule of thumb time. In consequence, when the complement has been on the side of excess, the majority of the tests come out negative.

One very seldom strikes the exact margin of complement wherein a positive result remains positive all day in the bath at 37°C . It must be remembered that the amount of complement-fixing substance present in gonococcal sera is much smaller than in the case of the Wassermann test. In gonorrhœa one can only expect to find very strongly positive reactions, which will remain positive in the water bath all day, in such cases as epididymitis, salpingitis and arthritis. At any rate, if any one gets a positive result which lasts for ten to fifteen minutes or longer after all the controls have gone, there is no reason for doubting or discarding that result.

After carrying out several thousands of complement-fixation tests in gonorrhœa, the whole mass of results has amply justified the writer's contention that such readings may be taken as definitely positive, even although they are of a transient nature.

Symbolic Representation of the Results.—When no hæmolysis occurs in the tubes A, B and C, the result is + + +.

When hæmolysis occurs in A but not in B or C, then it is + + -.

If hæmolysis occurs in A and B but not in C, it is + - -.

Transition stages in hæmolysis can also be recorded; for example, where only partial hæmolysis occurs in a tube it may be represented as \pm .

In the writer's table of results the following variety of symbols are given :—+ + +, + + -, + ± -, + - -, and - - -.

Those cases which give a + - - reaction should probably be considered as negative, unless there is definite clinical evidence of the disease as well.

ANALYSIS OF THE RESULTS OBTAINED IN 1031 CASES OF GONORRHOEA IN THE MALE.

Nature and Duration of the Disease.	No. of Cases Tested.	Strength of Reaction (Percentage Results).				
		+++	++-	+±-	+--	- - -
		Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Acute urethritis, 1 to 7 days	86	10.5	20	11.5	10.5	11.5
" " 7 to 14 days	75	3.3	37	8	15	7
" " 14 to 21 days	88	61	20	7	8	4
Sub-acute urethritis, 4 to 6 weeks	104	80	17	0	2	1
Chronic urethritis, including prostatitis and littritis, 6 weeks to 6 months	100	80	16	1	3	0
Chronic gleet (morning drop), 6 months to 1 year	93	43	20	3	19	15
" " " 1 to 5 years	83	33.5	9.5	7	21.5	25.5
Venereal warts	9	22	22	0	34	22
Acute epididymitis, 1 to 30 days	74	69	17.5	0	7	6.5
Sub-acute epididymitis, 1 month and over	46	76	17.5	0	2	4.5
Acute arthritis, 1 to 30 days	20	75	20	5	0	0
Chronic arthritis, 1 to 12 months or longer	33	58	30	0	6	0
Recurrent iritis cases	6	50	33	0	17	0
Cases clinically cured for 1 to 3 months	90	2	19	10.5	49.5	19
" " " 3 to 6 "	50	0	4	4	34	58
" " " 6 to 12 "	34	2.5	2.5	2.5	15.5	77
" " " 1 year and over	34	0	5	0	9	86
Total cases	1031					

ANALYSIS OF THE RESULTS OBTAINED IN 241 CASES OF GONORRHOEA IN THE FEMALE.¹

Nature and Duration of the Disease.	No. of Cases Tested.	Strength of Reaction (Percentage Results).				
		- - -	- .	+±-	+--	- . .
		Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Discharge from urethra, vagina or cervix (1 to 14 days)	15	20	20	6.5	33.5	20
Ditto (2 to 6 weeks)	38	63	29	5	0	3
" Chronic (6 weeks to 6 months)	59	67.5	17	0	9	6.5
" (6 months to 1 year)	36	70	30	0	0	0
" (1 to 5 years or more)	58	43	29.5	5	10	12.5
Salpingitis and ovaritis	12	91.5	8.5	0	0	0
Venereal warts	2	0	50	0	0	50
Cases clinically cured for 3 months	8	0	12.5	25	25	37.5
Cases clinically cured for 6 months or longer	13	0	0	0	30	70
Total cases	241					

¹ For this research the author is much indebted to the co-operation of Dr. Morna Rawlins.

ANALYSIS OF THE RESULTS OBTAINED IN 200 PERSONS GIVING NO HISTORY OF GONORRHOEA.

Notes and Remarks on the Condition of Persons Tested.	No. of Cases Tested.	Strength of Reactions (Percentage Results).				
		+++	++	+	-	---
Cases of chemical urethritis and no evidence of gonorrhœa	3	0	0	0	0	100
<i>B. coli</i> cystitis (no gonorrhœa)	2	0	0	0	0	100
Discharge of sterile pus (no gonorrhœa)	2	0	0	0	0	100
Urethral polypus (no gonorrhœa)	1	0	0	0	0	100
Swollen testicle due to trauma with no evidence of gonorrhœa	2	0	0	0	0	100
Tubercular epididymitis	2	0	0	0	0	100
Hydrocele (no gonorrhœa)	1	0	0	0	0	100
Infected scrotum (streptococcal)	1	0	0	0	0	100
Chronic rheumatism or rheumatoid arthritis (no history or evidence of gonorrhœa)	6	0	0	0	0	100
A case of scleroderma (no history of gonorrhœa)	1	0	0	0	0	100
Leucorrhœa slight (no suspicion of gonorrhœa)	6	0	0	0	0	100
Chronic leucorrhœa or purulent discharge with no evidence of gonorrhœa	8	0	0	0	0	100
Cases of syphilis who deny having had gonorrhœa	89	12	5.5	0	19	62.5
Normal persons with no history of gonorrhœa or syphilis	62	0	0	0	12	88
Total	200					

If we take the above tables and simplify them by taking the first three columns as positive results and the last two as negative, then we obtain the following percentages:—

Gonorrhœa in the Male.

Acute uncomplicated urethritis (1-7 days' duration)	42%	positive and	58%	negative.
" " " (7-14 " ")	78%	"	22%	"
" " " (14-21 " ")	88%	"	12%	"
Subacute " " (4-6 weeks' " ")	97%	"	3%	"
Chronic urethritis complicated with prostatitis, folliculitis, littritis, etc. (6 weeks to 6 months' duration)	96%	"	4%	"
Chronic gleet (with occasional morning drop lasting from 6 months to 1 year)	66%	"	34%	"
Ditto (lasting 1 to 5 years)	50%	"	50%	"
Venereal warts (no other signs)	44%	"	56%	"
Acute epididymitis (1 to 30 days' duration)	86.5%	"	13.5%	"
Subacute epididymitis (1 month and over)	93.5%	"	6.5%	"
Acute arthritis (1 to 30 days' duration)	100%	"	0%	"
Chronic arthritis (1 to 12 months or longer)	94%	"	6%	"
Recurrent iritis cases	83%	"	17%	"
Cases clinically cured for 1-3 months	31.5%	"	68.5%	"
" " 3-6 months	8%	"	92%	"
" " 6-12 months	7.5%	"	92.5%	"
" " 1 year and over	5%	"	95%	"

Gonorrhœa in the Female.

Urethritis, vaginitis, or cervicitis (1-14 days' duration)	46.5%	positive and 53.5% negative.
Urethritis, vaginitis, or cervicitis (2 to 6 weeks' duration)	97.0	„ 3.0 „
Urethritis, vaginitis, or cervicitis (6 weeks to 6 months' duration)	84.5	„ 15.5 „
Urethritis, vaginitis, or cervicitis (6 months to 1 year's duration)	100%	„ 0% „
Urethritis, vaginitis, or cervicitis (1 to 5 years and over)	77.5	„ 22.5 „
Salpingitis and ovaritis	100%	„ 0% „
Venereal warts (no other sign)	50%	„ 50% „
Cases clinically cured for 3-6 months	37.5	„ 62.5 „
Cases clinically cured for 6 months and over	0%	„ 100% „

Persons giving no history of Gonorrhœa.

Chemical urethritis with no evidence of gonorrhœa	0%	positive and 100% negative.
<i>B. coli</i> cystitis with no evidence of gonorrhœa	0%	„ 100% „
Discharge of sterile pus with no evidence of gonorrhœa	0%	„ 100% „
Urethral polypus with no evidence of gonorrhœa	0%	„ 100% „
Traumatic epididymitis with no evidence of gonorrhœa	0%	„ 100% „
Tubercular epididymitis with no evidence of gonorrhœa	0%	„ 100% „
Hydrocele with no evidence of gonorrhœa	0%	„ 100% „
Infected scrotum (streptococcal) with no evidence of gonorrhœa	0%	„ 100% „
Chronic rheumatism with no evidence of gonorrhœa	0%	„ 100% „
Scleroderma with no evidence of gonorrhœa	0%	„ 100% „
Slight leucorrhœa with no evidence of gonorrhœa	0%	„ 100% „
Chronic leucorrhœa or purulent discharge with no evidence of gonorrhœa	0%	„ 100% „
Cases of syphilis who deny gonorrhœa	18.5	„ 81.5 „
Normal persons with no evidence of gonorrhœa or syphilis	0%	„ 100% „

Reasons for taking the + - - Columns as Negative.—If complement-fixation tests are carried out on a series of bloods from persons who certainly never had gonorrhœa, it will be found that certain of the sera will show a negative reading before the others. Thus out of six negative sera perhaps four will show a complete negative with hæmolysis in all tubes, whilst the other two will show a + - - reaction, which, however, will change to a complete negative reaction after standing for a short time. It would appear, therefore, that with normal sera some show the negative result more quickly than others. Since the results of the complement-fixation tests by the author's method are read when the negative control tubes have completely hæmolyzed, it is easy to understand that if a very quickly acting negative serum control were employed, then certain sera which were really negative might give a + - - result. For this reason it is better to give all + - - reactions the benefit of the doubt and consider them negative, though undoubtedly many of these cases may be interpreted as suspicious. The history of the case is important in interpreting the result obtained. Thus in the first week of gonorrhœa one would hardly expect the blood to show more than a mere trace of positiveness, since sufficient anti-substance has not yet developed.

Comments and Conclusions regarding the above Analysis of Results.—(1) The first point worthy of note is the gradual development of anti-substance from the first week till about the sixth week of the disease. This is noted in the case of both the male and the female.

(2) The reverse occurs in the clinically cured cases, where it is clearly shown that the anti-substance gradually disappears as time goes on. Special investigations on this point have shown that after cure the patient loses the positive reaction slowly. As a rule one + is dropped every month or two. So that a +++ case after cure should be ++ - after one to two months, + - - after two to four months, and - - - after three to six months.

A fall in the amount of positiveness from month to month indicates that the patient is cured. If, however, the positiveness remains level from month to month this would indicate that the disease still remains.

(3) It is interesting to note that all complicated cases such as epididymitis, salpingitis and arthritis give the highest percentage of positive reactions, and these reactions are always stronger than in the case of mucous membrane affections. Epididymitis cases very often give a + + + + + or even a six-positive reaction.

It will appear, therefore, that the mucous membranes have not such a high power of producing anti-substances as certain other tissues. It will also be noticed that certain of the epididymitis cases gave completely negative results. The author believes that in such cases the gonococcus could not have been responsible, and there is no doubt that sometimes the epididymis is attacked by one or other of the secondary infections which occur in gonorrhœa, such as diphtheroids and *B. coli*, etc. Cases of traumatic epididymitis, tubercular epididymitis, and cases of ordinary hydrocele always give negative reactions.

(4) In gonorrhœal rheumatism very nearly 100 per cent of the cases gave a definite positive reaction, whereas other cases with ordinary rheumatism and rheumatoid arthritis always give a negative result. This is sufficient to show that the test is a powerful diagnostic agent.

(5) All persons giving no history of gonorrhœa showed 100 per cent of negative tests, with the exception of the syphilis cases. Amongst the syphilitics who denied gonorrhœa, 18.5 per cent gave positive reactions to the gonococcal antigen. Further investigation, however, of these cases proved that at least 10 per cent of them showed clinical signs of gonorrhœa on examination of the prostate and the urine. Some actually showed the gonococcus in smears from the urethra, and a few admitted later that they had had the disease. It is obvious therefore that a patient's denial of gonorrhœa is not of much value.

(6) Certain cases of leucorrhœa, and even of chronic purulent discharge in females, constantly show a negative complement-fixation test, which indicates that some of these conditions are not necessarily gonococcal in nature.

(7) The complement-fixation test for gonorrhœa, when carried out with careful controls, using a good antigen, and the long-fixation method in the ice-chest, is extremely delicate, and compares very favourably with even the Wassermann test in syphilis. With regard to the diagnosis of gonorrhœa in women it is invaluable. The author's experience shows that one seldom finds the gonococcus by microscopic examination in more than 10 per cent of smears from suspected females. With the complement-fixation test, on the other hand, 90 per cent of positive results are obtained, that is to say, if one were to rely on microscopic examination alone one would miss 80 per cent of the cases. Furthermore, the microscopic examination is almost valueless as a test of cure, since it is almost impossible to find gonococci in old chronic discharges in the female, even after provocation with silver nitrate.

(8) Finally, the gonococcal complement-fixation test is invaluable as a diagnostic agent in cases of rheumatism, salpingitis, ovaritis, etc., and is of the greatest value in all cases, both male and female, as a test of cure of the disease.

Confirmation of the Author's Results. After writing this chapter, the author received two letters from Capt. A. W. Hunter, C.A.M.C., giving an account of his own researches on the subject. In 1918 at the Military Hospital, Rochester Row, London, S.W., this officer learnt how to prepare the new gonococcal antigen, as well as the writer's technique for carrying out the complement-fixation test.

Since that time he has carried out a large number of complement-fixation reactions with cases of gonorrhœa in the Canadian army in England and later in Canada.

In his first letter, dated Toronto, 28th October 1919, he states :—

I have now grown fourteen or more varieties of the gonococcus and have made up the new compound antigen. At present I am trying it out on women. The first 18 cases of clinical gonorrhœa showed the following results :—Sixteen were + + +, one was + +, and one was + - -.

Dr. B. P. Watson, Professor of Gynæcology (now in Edinburgh), supplied the cases.

The partial review of my work in England shows the following results :—

Nature of Cases.	Percentage Results.				Totals.	
	+ + +	- - -	+ - -	- - -	Positive.	Negative.
Acute simple gonorrhœa up to 8 weeks' duration	Per cent. 54·61	Per cent. 16·92	Per cent. 10·76	Per cent. 17·71	Per cent. 82·29	Per cent. 17·71
Acute complicated gonorrhœa	53·84	23·07	15·38	7·71	92·29	7·71
Chronic simple gonorrhœa, <i>i.e.</i> over 8 weeks' duration	53·77	19·33	14·62	12·25	87·72	12·28
Chronic complicated over 8 weeks' duration	59·7	22·38	11·94	5·98	94·02	5·98

In a total of 422 cases with complete clinical records and clinically gonorrhœa, 87 per cent were positive.

I thought these results would interest you. In fact, they show the highest numbers of positives of any records obtainable. Warden and Schmidt are coming up well, but his antigen (lipoidal) is not so good as yours.

In his second letter, dated Montreal, 17th January 1920, Capt. Hunter says :—

The new antigen which I made from the Canadian infections has worked well. I will give you a few of my results :—Forty-five women with clinical gonorrhœa, acute and subacute, showed the following reactions :—82 per cent + + + ; 9 per cent + + ; 4·5 per cent + - - ; *i.e.* a total of 95 per cent were positive.

With regard to men the following results were obtained :—

Nature of Cases in Men.	Percentage Results.			
	+ + +	+ - -	- - -	- - -
	Per cent.	Per cent.	Per cent.	Per cent.
Acute simple gonorrhœal urethritis (8 weeks or less)	55	17	11	17
Acute complicated gonorrhœal urethritis (8 weeks or less)	54	24	15	7
Chronic simple (8 weeks and over)	54	20	14	12
Chronic complicated	60	23	11	6
Acute rheumatism	67	22	2	11

Four cases showed positive results within seven days of the onset of symptoms, 50 per cent being + + + and 50 per cent + +. Eighteen non-complicated cases showed a positive reaction within fourteen days of the onset of symptoms in 88 per cent. Clinically non-gonorrhœa cases were always negative.

From the above notes from Capt. Hunter's letters it is obvious that his results agree

very closely with those of the author, and it is further apparent that the results obtained by both of us are far superior to those hitherto obtained by any previous worker on the subject.

This superiority in the delicacy of the results is undoubtedly due in the first place to the improved antigen used, and in the second place to the superiority of the ice-chest method. The writer has repeatedly carried out two series of gonococcal fixation tests with the new antigen.

Series (1) carried out by the long-fixation method in the ice chest.

Series (2) carried out by the usual short-fixation at room temperature and in the water bath at 37.5° C.

The number of positive results obtained in series (1) was invariably higher than in series (2).

Further Experimental Researches on the Complement-Fixation Test.—Professor Dean has shown that the absorption—or rather adsorption—of the complement is due to the formation of a fine and almost invisible precipitate. This fine precipitate is formed as the result of the union of the colloid particles of the antigen with those of the anti-substance present. If anti-substance towards the specific antigen is not present in the serum, then no precipitate is produced, and in consequence the complement is not adsorbed.

As already stated, the author's gonococcal antigen consists of a nearly neutral solution of the gonococci.

If this dissolved antigen is brought to a slightly acid reaction a precipitate is produced.

Moreover, it is also precipitated by the addition of certain salts such as calcium chloride and sodium chloride.

It is reasonable to suppose therefore that if a given negative serum was rendered slightly acid, or if a trace of calcium chloride was added to it, then that serum would be rendered positive, since it would be able to form a fine precipitate when mixed with the gonococcal antigen, and thereby the complement would be adsorbed.

Experiment 1.—Gonococcal complement-fixation tests were carried out in the usual manner with a known negative serum to which varying quantities of calcium chloride had been added.

Results :—

Negative serum plus	0.1%	calcium chloride give a	- - -	reaction.
" "	0.2%	" "	- - -	"
" "	0.3%	" "	- - -	"
" "	0.4%	" "	+ - -	"
" "	0.5%	" "	+ + +	"
" "	1%	" "	+ + +	"

In another series of experiments a negative serum gave a + + - reaction with the addition of only 0.125% calcium chloride. It was also found that the addition of 0.6% acid sodium phosphate (NaH_2PO_4) to a negative serum rendered it positive.

In the above tests the serum control tubes hemolysed in the usual way, which showed that the addition of the chemicals to the serum did not in itself render them anti-complementary. Later it was found that the addition of sodium chloride to a negative serum was also capable of changing its reaction to positive. It required larger amounts of NaCl than in the case of calcium chloride, however, to cause this result.

Experiment 2.—Gonococcal complement-fixation tests were carried out in the usual manner with a negative serum to which varying quantities of sodium chloride had been added. The results were as follows :—

Negative serum plus 0.85% NaCl: result	- - -
" " 1.0%	" " - - -
" " 1.5%	" " - - -
" " 2.0%	" " + - -
" " 2.5%	" " - - -
" " 5%	" " + + +
" " 10%	" " + + +
" " 20%	" " + + +

These results are sufficient to show that in carrying out the complement-fixation tests it is very necessary to use clean tubes which are not contaminated by any chemical, such as acid, etc. Also that the dilution of the sera to be tested should not be carried out with a saline solution which is stronger than normal, viz. 0.85 per cent.

Having ascertained these facts it occurred to the author that the negative serum of a given individual might be induced to show a positive reaction, after the individual had swallowed a considerable dose of calcium chloride.

Experiment 3.—A sample of the writer's blood was taken for the complement-fixation test about one hour before lunch. Fifteen grains of calcium chloride in water (on an empty stomach) were then swallowed, and another sample of blood was taken half an hour later. Six hours later a third sample of blood was taken.

The gonococcal complement-fixation test was carried out simultaneously on these three samples of blood with the following results:—

Serum before swallowing calcium chloride - - - reaction.
 Serum half hour after swallowing calcium chloride + + + reaction.
 Serum six hours after swallowing calcium chloride + - - reaction.

This experiment was repeated the following day and gave practically the same results:—

Before calcium chloride - - - reaction.
 Half hour after calcium chloride + + - reaction.
 Six hours after calcium chloride - - - reaction.

Later this experiment was repeated on three volunteers with negative sera. In two of these the serum became temporarily positive after the calcium chloride; in the third the reaction of the serum was not affected.

Experiment 4.—It is generally believed that the specific anti-substances formed in the system towards germs are colloids and probably proteins. It is just possible, however, that calcium and other salts might be present in the protein anti-substances, and that the calcium or other salt content might be responsible for the precipitation of the specified antigen.

If such were the case it was conceivable that chemicals which precipitated calcium or other salts would remove or precipitate the anti-substances from the serum.

The following experiments were carried out to prove or disprove this idea:—

(1) A known positive gonococcal serum was treated with varying quantities of a solution of ammonium oxalate in order to cause precipitation of any calcium compounds present.

(2) A known positive gonococcal serum was treated with varying quantities of silver nitrate in order to precipitate any chloride compounds present.

After treatment with these chemicals the positive sera were allowed to stand and were then centrifugalised.

Complement-fixation tests were now carried out with the positive sera so treated, in the usual way. Positive reactions were still obtained. This was sufficient to show that the anti-substances present were not precipitated or removed from the positive sera by the addition either of ammonium oxalate or of silver nitrate.

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PART IV

VACCINE THERAPY, SERUM THERAPY, CHEMICAL THERAPY, ELECTRO- AND THERMO-THERAPY

CHAPTER XXX

ACTIVE IMMUNISATION BY VACCINE THERAPY

THE literature on the vaccine treatment of gonorrhœa is enormous. The writer has collected some 270 references, but these must only represent a fraction of the total articles on the subject.

The purpose of vaccine therapy is to stimulate the formation of specific anti-substances artificially by inoculation of the dead germs into the patient. In the previous chapters sufficient scientific evidence has been brought forward to show that agglutinins, precipitins, bacteriolysins and complement-deviating substances are developed in the blood of man and animals by subcutaneous or intra-peritoneal inoculations of gonococci. The scientific reasons for vaccine therapy are based upon sound facts demonstrated by thousands of experiments made with almost every species of pathogenic organism. The evidence brought forward by the vast total of these experiments has proved beyond all doubt that when animals, including man, are inoculated with bacteria and other foreign proteins, such as red cells, etc., there is almost invariably produced, as a direct result of the inoculation, specific anti-substances towards the bacterium or foreign protein injected.

In some cases the amount of immunity produced even by a few successive inoculations is very great, and this immunity may continue for a year or more. In spite, however, of the colossal amount of evidence now at hand which proves these statements to be beyond all question, there are still a few individuals, even amongst the medical profession, who would appear to believe that vaccines are of mythical value, and that the evidence existing as to their therapeutic and prophylactic power is purely theoretical.

This prejudice against vaccines is due partly to ignorance regarding the vast number of experiments which have been made by thousands of workers on the subject, and also partly to lack of accurate clinical observation on the part of those who attempt to use them. It is due also to fallen expectations. When vaccines were first introduced it was expected that they would perform miracles. The miracles, however, were rare, so faith dwindled, and a kind of revolt set in. We find medical men even now trying to explain the therapeutic effect of vaccines as being due merely to reaction, temperature, etc., caused by the inoculation, and we find these observers advocating in various diseases inoculations of certain germs such as typhoid bacilli, in conditions entirely different from typhoid fever. Treatment with the so-called "phylacogens" and injections of milk come more or less under the same category. Whether those who advocate the use of these non-specific inoculations are aware of the vast number of experiments by eminent

workers, showing that injections of an organism produce specific anti-substances to that organism, one cannot tell. If they have a definite knowledge of these scientific researches, why do they ignore them and attempt to attribute the therapeutic results obtained to other causes; and if a temperature reaction is of value why not produce that reaction by the specific organism in question? It is almost as bad as advocating the injection of ox corpuscles into a rabbit in order to produce a specific hæmolysin to the red corpuscles of a sheep. If anti-substances to sheep corpuscles are desired, why not inject sheep corpuscles, instead of other foreign substances? Although the medical profession on the whole is becoming very rapidly conversant with these matters, the non-medical classes show an extraordinary state of ignorance, and have very curious ideas on the subject. It would also appear that they have been told by certain physicians that vaccines are useless. About five years ago, whilst the author was busy making up a large quantity of vaccine for the army, a clergyman visited him in the laboratory. He evidently thought that the writer was wasting his time, since he asked if vaccines were of any use? The author pointed out to him that his question was tantamount to inferring that one who made vaccines was a charlatan, and the writer further explained that he was not in the habit of making up substances which he considered to be of no value. This answer was of course very bad, as one should rather have attempted to explain the whole matter to him. He fled precipitately, however, leaving the writer to regret his display of irritation.

In order to avoid committing such an error whilst writing this book, it will be wise to give the opinions of various clinical observers as to the value of gonococcal vaccine. Thereafter the author's own researches on the subject will be given, in the hope that they may be instructive and interesting to the reader.

The first attempts to treat gonorrhœa with vaccines were made about the year 1907. In that year Wollstein, following the researches of Flexner on the meningococcus, showed that injections of dead gonococci into animals produced specific agglutinins and complement-deviating substances.

Cole and Meakins (1907) reported on 15 cases of gonorrhœal arthritis treated by vaccine therapy, which they had studied throughout the entire course of the disease. They administered by subcutaneous injection doses of 300 million gonococci, increasing gradually, with seven- to ten-day intervals, to 1000 million. A total of four doses was given in twenty-nine days. The opsonic index rose from 0.2 to 2 in some cases.

It was advocated that the vaccine should be made from young cultures not more than twenty-four hours old. They did not find that autogenous vaccines presented any superiority over stock vaccines. No ill effects resulted from the injections beyond a slight local reaction with pain and redness. In their opinion the treatment appeared to be of distinct value. Ten cases were cured and 5 improved. Ohlmacher (1907) used gonococcal vaccine in 2 cases of gonorrhœal arthritis; 1 was cured and the other improved. M'Arthur (1907) treated 1 case with the same complaint and obtained a cure.

Vail (1907) made 300 opsonic index estimations on thirty normal individuals, and found that the opsonic index to the gonococcus ranged from 0.8 to 1.2, and that the phagocytic index ran closely parallel to the opsonic index. In gonorrhœal patients, the injection of repeated doses of 10 million gonococci in adults and 4 to 8 million in children, raised both the phagocytic and opsonic indices very satisfactorily. Only two injections of vaccine (in a series of 52 cases) were followed by a negative phase in the opsonic index, but Vail was unable to note any clinical negative phase after the doses mentioned.

Churchill and Soper (1908) treated 41 cases of gonococcus vulvo-vaginitis in children with vaccine, and concluded that vaccines were instrumental in shortening the stay of the patients in hospital. They obtained a permanent cure after an average treatment of nineteen days. Doses of 5 to 120 millions were used for the oldest girls, and 5 to 60 or 80 millions for girls five years of age. After the injections they noted a fall in the opsonic index for a day or two, followed by a rise. They thought that vaccines prepared

from old strains of gonococci gave better results than those made from freshly isolated strains. In their opinion it is desirable but not necessary to control the injections with opsonic index estimations.

Hamilton and Cooke (1908) also treated cases of vulvo-vaginitis in little girls with doses of 5 to 10 millions, increasing gradually to 20 to 25 millions. They got improvement in acute cases, and a shortening of the later stages. In chronic cases the good effects were still more evident. The opsonic index was found to be lower than normal in both the acute and chronic cases, averaging from 0.44 to 0.62. After an injection of vaccine the index fell on the average to 0.37, followed later by a sharp rise. The highest opsonic index obtained after vaccine treatment was 1.9. They did not consider that estimation of the opsonic index was necessary for practical purposes. Like Churchill and Soper, they got better results with vaccine prepared from gonococci which had been grown for long periods than from fresh strains.

Butler and Long (1908) treated 12 cases of infantile gonorrhœal vulvo-vaginitis with polyvalent stock vaccine, and compared these with other 12 cases treated locally with potassium permanganate. They found that the vaccine produced very rapid improvement and often recovery, and that it was more effective than the local antiseptic applications. With the vaccine they obtained 11 cures after an average treatment of thirty-nine days. In 4 cases the symptoms disappeared in ten days to three weeks, but some required a prolonged course of inoculations. They had 70 per cent of cures in acute cases. The dosage was commenced at 5 millions, and gradually increased every fifth or sixth day up to 50 or 100 millions. They did not think that the larger doses were any more efficacious than the smaller. They did not find any value in anti-gonococcal serum.

Ballenger (1908) reported excellent results with gonococcal vaccine in 26 cases of gonorrhœa, most of which had complications—8 chronic and 2 acute prostatitis, 2 epididymitis, 3 urethro-cystitis, 1 cystitis, and 1 peri-urethral abscess. He gave doses of 5 millions, increasing to 50 millions in acute cases, and larger doses, commencing with 15 millions, in chronic cases. Improvement usually commenced in five to eight days after the first injection. Five to eight injections were required to cure most cases. He advocates local treatment as well, with massage and evacuation of abscesses. He also draws attention to the necessity of careful microscopic examination of the urethral discharge, in order to test for the presence of other secondary microbial infections. When the latter occur, the appropriate vaccine should be given along with the gonococcal vaccine. He maintains that at the time of the negative phase following the vaccine, massage of the prostate and manipulation of the joints in arthritis cases should be avoided, as this may tend to produce a further auto-inoculation with the germs.

Aronstam (1908) obtained beneficial results with stock gonococcal vaccine in acute cases of urethritis, which were cured in about four weeks. He considers the vaccine to be curative in epididymitis, acute prostatitis, Cowperitis and adenitis, and also got good results in cases of iritis. In arthritis it shortened the course of the illness and brought about a speedy cure. It did not always act well in chronic urethritis cases. In these he usually found it necessary to give a mixed vaccine of staphylococci and gonococci. He usually gave a dose of 20 to 40 million gonococci, but no rule could be laid down as regards dosage, as this depended upon the reaction produced in each individual case. The negative phase lasted for two or at the utmost three days.

Irons (1908) reported on 40 cases of which 31 suffered from arthritis. Of the latter, 18 were cured and 9 were improved by gonococcal vaccine. On the other hand, 4 cases did not appear to be benefited by it. With regard to acute urethritis the vaccine did not appear to be of any marked clinical value, but he considered that it had a markedly beneficial effect in chronic cases. He believed in doses ranging from 100 to 1000 millions every three to seven days; doses of 20 to 50 millions were regarded as too small to be of much value. He used stock vaccines, consisting of three to four strains of twenty-four-

hour cultures. Each injection caused a sharp rise in the opsonic index. This rise was also produced after massage of the prostate or affected joints. He explains this as due to an auto-inoculation with the germs. There was generally a negative phase, indicated by a slight rise of temperature, increased pain and tenderness in the joints about twenty-four hours after the vaccine inoculation. Often there was a considerable tenderness and redness at the site of the injection, and sometimes also a feeling of general malaise. These reactions, however, were not so noticeable when the doses were increased gradually. He found that the best therapeutic results were obtained when the doses were just sufficient to produce a slight clinical reaction. Eight adults with no history of gonorrhœa were injected with doses of 500 millions without any reactions.

Ohlmacher (1908) often found diphtheroid bacilli of the xerosis type associated with the gonococcus in cases of chronic urethritis. In these cases good results were obtained with a mixed vaccine of both germs. The diphtheroids readily disappeared as a result of the inoculations.

Rosenow (1909) described a case of ulcerative cystitis in a woman, due to a bacillus of the pseudo-diphtheria type. The serum showed a high agglutination power against this bacillus. The condition was cured by drainage of the bladder, and by an autogenous vaccine given in doses of 50 to 500 millions.

Whitmore (1908) found that stock gonococcal vaccines of three or four strains injected every seven to ten days were valuable in arthritis, but he did not express an opinion as to their value in urethritis.

Bristow (1908) cured 1 case, and Illman (1908) cured 2 cases of gonorrhœal rheumatism with gonococcal vaccine alone. Kinnear (1908) found vaccine valuable in cases with epididymitis.

In 1909 Parsche, Robinson and Ebright reported on the treatment of gonorrhœa with vaccines, but the writer has been unable to gain access to their work.

Dieulafoy (1909) referred to 2 cases of gonococcal septicæmia treated with vaccine with good success.

Bosanquet and Eyre (1909), and also Emery (1909), speak positively and enthusiastically of the curative effects of gonococcal vaccine in all forms of gonorrhœa. Pollock (1909) and Hartwell (1909) state that it is of no value in cases of urethritis. With regard to arthritis the latter treated 51 cases. Of these none were definitely cured, 42 were improved, and 9 appeared to be uninfluenced.

White and Eyre (1909) treated 4 cases of gonococcal arthritis with gonococcal vaccine, and claim that all were cured. They consider that autogenous vaccine was more efficacious than stock vaccine.

Eyre and Stewart (1909) treated 43 cases, both males and females, including simple acute and chronic gonorrhœa, gonococcal septicæmia and sapræmia, epididymitis, iritis and arthritis. They used cultures twenty-four hours old, emulsified in 0.1 per cent saline and 0.25 per cent trikresol and heated to 50° C. for one and a half hours. The following summary is taken from their work on the subject :—

- (1) Gonococcal vaccine is markedly toxic and excites a profound influence on the disease.
- (2) It is not devoid of danger, and requires considerable caution.
- (3) Polyvalent stock vaccine (twelve strains) is only slightly inferior to autogenous vaccine.
- (4) Small doses given often are better than large doses given at longer intervals.
- (5) Small doses of 1 to 10 millions are safer and more satisfactory than doses of 50 to 100 millions.
- (6) With doses of $\frac{1}{2}$ to 2 millions the negative phase is absent or very transient.
- (7) With doses of 5 to 10 millions the negative phase lasts about forty-eight hours, and the positive phase lasts from three to five days.
- (8) Small doses steady and raise the opsonic index. A steady opsonic index just above normal is the best condition for rapid recovery.
- (9) Simple chronic urethritis cases with mixed infection are more difficult to cure with gonococcal vaccine than those in which there are no secondary organisms.

(10) In cases of chronic gonorrhœa with complications doses of 1 to 2 millions every three to five days, 5 millions every five to seven days, and 10 millions every eight to ten days, are safe and satisfactory. Larger doses are seldom desirable, and the use of larger doses is even more dangerous in chronic than in acute cases.

(11) In epididymitis small doses quickly relieve the pain and cause rapid improvement.

(12) In iritis cases the severe pain is relieved in forty-eight hours, disappears in three to four days, and the cure is hastened.

(13) Of 26 arthritis cases treated, 18 were cured and 8 improved.

Hale White (1909) records 4 cases of gonococcal arthritis, 2 of which were rapidly cured with vaccine in three to five weeks by three doses of 5 to 10 millions, the third by four doses of 5 to 25 millions, and the fourth by three doses of 100 to 200 millions.

Ladd and Russ (1909) treated 11 cases of arthritis with vaccine; all of these were improved.

Oastler (1909) treated 1 case and obtained a cure with vaccine alone.

Mauté (1909) treated 4 cases of arthritis with vaccine and all were cured. He considered that urethral gonorrhœa was also affected favourably.

Mainini (1909) reported on the results of vaccine in 6 cases of gonococcal arthritis. He states that it arrests the pain, but that it did not seem to modify the course of the disease in the sense of curing it. He suggests that the specific action on the pain in true gonococcal rheumatism might be useful in differentiating this disease from other allied joint affections.

M'Oscar (1909) obtained good results in joint affections.

Dieulafoy (1909), out of 18 arthritis cases, got 7 cures with vaccine. Eight cases were improved and 3 did not seem to derive any benefit. He considered that the vaccine was valuable in cases of gonococcal septicæmia, more especially when controlled by the opsonic index.

Loxton (1909) recorded good results in 3 cases of chronic gonorrhœa treated with gonococcal vaccine prepared by the Lister Institute. He gave doses of 40 to 50 millions, and increased the amount rapidly either by reducing the interval between injections or by augmenting the dose.

Moncure (1909) states that vaccine is beneficial in chronic gonococcal arthritis, but that adhesions of course were not in the least amenable and required operative treatment.

Bruck (1909) considered that gonococcal vaccine could induce active immunity, and that it was valuable in complications such as epididymitis and arthritis, and in general infections which frequently proved refractory to the ordinary measures. A case of vulvo-vaginitis was improved by the vaccine, but cases of acute and chronic urethritis and prostatitis were apparently unaffected. He did not consider that vaccine treatment was dangerous.

Baumann, and also Crockett (1909), got good results with vaccine treatment in gonorrhœa.

Lake (1910) treated a single case of chronic gonorrhœal urethritis with stock gonococcal vaccine. He gave three doses of 15 millions, three of 25 millions, and three of 40, 60 and 75 millions respectively. He thought that the vaccine caused increased phagocytosis, but it did not appear to produce any favourable effect on the course of the disease. On the other hand, it caused no bad effects.

Ssowinski, Jarvis, Jamieson and also Miller (1910) claimed that the vaccine had a valuable influence on urethral gonorrhœa. The latter observer also treated one case of arthritis and obtained a cure.

Boas and Wulff, Beckwith, and also Butler (1910), obtained good results with vaccine in infantile gonorrhœal vulvo-vaginitis.

Hamilton (1910) claimed that in cases of vulvo-vaginitis in children, gonococcal vaccine was the best mode of treatment. She treated two parallel series of cases, one series with irrigation alone, and the other series with vaccine alone, with the following results :—

Treatment.	No. of Cases.	Cured.	Uncured.	Lost Sight of.	Percentage Cured.
Irrigation	260	158	53	49	60
Vaccine	84	76	5	3	90

The children were not considered as cured until they were free from gonococci by microscopic examination (Gram's stain) for four weeks—one examination per week.

The average length of time under active treatment by the irrigation method—260 cases—was 10·1 months. The average length of time under active treatment by vaccine—84 cases—was 1·7 months.

Nineteen of the vaccine-cured cases were followed for three months, and there was no evidence of relapse in any.

Stock vaccines were used. In the majority of cases she commenced with a dose of 50 million gonococci, increasing by increments of 10 millions every fifth day, until the dose reached 90 millions. Thereafter a dose of 100 millions and upwards was injected every tenth day. In some the dose was increased to 200 millions, and in one child aged eight a dose of 1000 millions was given without appreciable reaction. In most of the acute cases six injections of vaccine were sufficient to bring about a cure. The old-standing chronic cases required longer treatment, sometimes up to eighteen injections.

She summarises the advantages of the vaccine treatment as follows :—

- (1) Only a short time is required for cure in over 85 per cent of cases.
- (2) It is easy to administer, no special apparatus or technique being required.
- (3) It is harmless when injected under aseptic precautions.
- (4) It is not necessary to take the opsonic index.
- (5) It eliminates irrigations, which direct the child's attention to its genitals, at times encouraging precocious masturbation. Moreover, frequent douches, carried out even with the greatest care and gentleness, will produce some injury when continued for a long period.

Lewin (1910), Schindler (1910), Schmidt, L. E. (1910), Champion (1910), Shropshire (1910), and Scott (1910), all obtained good results with gonococcal vaccine, more especially in complications such as epididymitis and arthritis.

Littlewood (1910) considered that the time was rapidly approaching when the vaccine treatment of gonorrhœa would supersede all other methods, both in acute and chronic conditions. The best results, however, seemed to be obtained in the chronic cases.

Myer Coplans (1910) stated that in chronic gleans, mixed infections were nearly always present, and that no two cases showed the same organisms. In his opinion the best results were obtained by isolating the organisms in each particular case, and by treating the patient with his own mixed autogenous vaccine. Variable results were obtained with vaccine in acute cases, and some had given up vaccine treatment in such cases.

Thomas (1910) maintained that he had seen miraculous results follow after the injection of vaccine in certain acute cases of gonococcal arthritis. He was convinced that the best results were obtained with autogenous vaccines prepared fresh every two to four weeks. In a further paper he reports on four cases of gonococcal arthritis, of which two were cured and two improved by vaccine therapy.

Allen (1910) speaks favourably concerning gonococcal vaccine, and recommends an initial dose of 500 millions, rising gradually to 1000 millions.

Miller and Jack (1910) treated 4 cases with autogenous vaccine with excellent results, a cure being obtained after three to four injections.

Doses of 4 to 10 millions were given.

Jack (1910) administered vaccine in doses of 4 to 10 millions to four gonococcal arthritis cases, and obtained a cure in all after a period of seventeen days to seven weeks. The number of injections required for cure was four to nine.

McDonald (1910) reported on 14 cases of gonorrhœal arthritis treated with vaccine. Nine were cured, 1 was improved, and 4 derived no benefit from it.

Hartwell (1910) similarly reported on a series of 51 cases of arthritis. These were treated where possible with autogenous gonococcal vaccine in doses of 100 to 600 million germs in the chronic cases, every five to seven days. In acute cases he gave 10 to 25 millions every two to four days, and later increased to 100 millions. He considered that the autogenous vaccines gave far better results than stock vaccines. He thought that there was not much evidence of immunity obtained from the first few injections, and certainly no lasting immunity was conferred.

Thirty-one of his cases were very chronic and crippled. Of these, 27 were discharged with complete functioning joints without disability. Stiff backs in 5 cases were very markedly improved. The vaccine, in his opinion, was very valuable, but did not seem capable of preventing extension to fresh joints in the early cases, neither did they produce sufficient lasting immunity to prevent recurrences.

Young (1910) treated 28 cases of gonorrhœal rheumatism with vaccine. The duration of the gonorrhœa prior to the onset of rheumatism in his cases varied from nine days to two years, and the duration of the rheumatism prior to his administration of vaccine was four days to six months. The number of vaccine injections ranged from one to fifteen, and the dosage varied from 5 to 50 millions injected subcutaneously into the groin at intervals of from two to fourteen days. Practically no other treatment was used. He claimed 20 cures and 5 improved. The remaining 3 cases did not seem to derive any benefit from the treatment.

Murrell (1910) reported on 3 arthritis cases which recovered, but not rapidly, under the influence of vaccine therapy.

Tuttle (1910) records a case of gonorrhœa of the genitals complicated with salpingitis which he treated successfully with large doses of gonococcal vaccine. Complete recovery was brought about in a month, and the patient gave birth to a healthy child after her recovery.

Shumway (1910) treated a case of gonorrhœal iritis successfully with gonococcal vaccine.

Murray (1910) reported on a case of gonorrhœal arthritis complicated with iritis. He administered two doses of 25 million gonococcal vaccine and one dose of 50 millions. The arthritis was benefited, but it had no effect on the iritis.

Bruck (1910) states that gonococcal vaccine is especially useful in cases of gonorrhœa with epididymitis and arthritis. The results were particularly good in 50 cases of the former. If there was no fever he injected vaccine at once. Where there was severe pain with fever, he sterilised the scrotum with tincture of iodine, incised the tunica and applied an alcohol dressing. This relieved the pain, and when the fever subsided vaccine therapy was commenced.

Friedländer and Reiter (1910) treated 25 cases of acute, subacute and chronic gonorrhœal epididymitis with Reiter's stock vaccine. Doses of 2 million gonococci were injected every two to three days, gradually increasing to 5 millions. Larger doses were avoided in order to prevent any rise of temperature. In the acute and subacute cases the swelling practically disappeared after three to five injections. The results obtained by the vaccine in acute catarrhal prostatitis were indefinite, but better effects were noticeable in cases of acute and chronic follicular prostatitis. In the latter, after the ninth injection the turbidity of the urine cleared up completely. In their opinion gonococcal vaccine was useless for resolving the fibrous remains of epididymitis. It was of no value in cases of acute and subacute urethritis (anterior and posterior) or in urethrocystitis. In these latter cases vaccine could not be compared in curative value to the modern silver preparations.

The following German observers, Klausner, Fromme-Collmann, Schultz, Rygier, Wolfsohn, Dembska, and Hansteen (1911) all reported favourably on gonococcal vaccine

therapy, more especially with regard to epididymitis and arthritis. Hansteen did not find that it gave any particular results in ordinary urethral gonorrhœa.

Schmitt, A. (1911) got good results with Reiter's vaccine, and also with "Arthigon"—a commercial German gonococcal vaccine—in vulvo-vaginitis, cervical gonorrhœa, epididymitis, prostatitis and spermato-cystitis. He was unable, however, to note any beneficial effect in urethral gonorrhœa.

Reiter (1911) was one of the first to use gonococcal vaccine in the routine treatment of women affected with the disease. He gave fairly small doses of about 5 millions, increasing gradually at intervals of not less than five days. He did not increase the amount if the previous dose had produced a definite reaction, and he avoided the use of vaccine in early cases with fever.

Bruck gave a more intensive treatment with somewhat larger doses.

Schindler (1911) did not consider that fever was a contra-indication to the administration of vaccine, provided the temperature was not very high. On the contrary, he thought that some fever was a good sign, as it indicated a reactive power in the body against the germ. He got good results with vaccine in cases of salpingitis.

Jelkin observed good results after a few injections of vaccine.

Menzer (1911) advises the immediate administration of vaccine, and also warm sitz baths as the routine treatment of acute gonorrhœa. He is convinced that this is the only way in which the disease can be effectually eradicated. He states that the aim in treatment is to favour, not to suppress the discharge. After the course of treatment the patient should be given a provocative dose of vaccine in order to test if he is really cured. If not, the vaccine course should be continued, along with special diet, rest and massage of the prostate. Cases of acute gonorrhœa should be kept in bed for two to three weeks. Gonococcal vaccine produces a focal reaction wherever there is a gonorrhœal process, and this has a curative reaction on the gonococci ensconced there. Finally, he states that vaccine is only an aid to treatment, and must not be relied upon alone to destroy all the germs or to ward off complications.

M'Neil, Köhler and MacKinney (1911) have written further papers on the subject.

Stockman (1911) treated nine patients suffering from arthritis; in all of these cases gonococci were isolated from the urethra, vagina or the joints. In all, vaccine alone was given at first, but in most of them no distinct improvement followed, and after waiting a reasonable time ordinary local treatment was usually superadded or substituted. This was always followed by immediate improvement both locally and generally, and finally led to cure. Only one case showed a rapid improvement after one dose of 5 million gonococci, and he thinks it likely that this was going to recover in any case. He varied the dose, but was unable to give the large doses recommended by Allen and others on account of the violent reaction which often followed even after much smaller quantities. He states that the usual duration of gonorrhœal arthritis is five to eight weeks, and he did not find that vaccine shortened this period. He concludes that vaccine exerts no curative influence on gonorrhœal rheumatism, that it is, in short, valueless as a practical clinical treatment. Although the above author is in disagreement with the majority of observers, it must be admitted that his paper is a careful one. He gives charts of all the cases.

Bain (1911) states that like Stockman he was not impressed with the success of vaccine treatment in the cure of arthritis following upon an attack of gonorrhœa.

Stower (1911) analysed the reports of the vaccine treatment of gonococcal arthritis, as given by nineteen different observers. Out of 195 cases treated with the vaccine, 84 were cured, 91 were improved, and 20 did not appear to be benefited.

Cattle (1912) urged the use of vaccines in chronic cases of gonorrhœa, especially where arthritis was present.

Murrell (1912) states that the only effective method of treating gonococcal arthritis was by vaccine, using an autovaccine. In some cases he had used large doses, even up

to 500 millions every three or four days. He was in agreement with the opinion that the dose for urethritis should be 75 millions, for iritis 250 millions, and for arthritis 500 millions; on the other hand, he is against large initial doses such as 825 millions. He agrees with Hartwell (1910), who found that autogenous vaccines were valuable in all stages of gonorrhœal arthritis, except when ankylosis has occurred. He cited one case of gonorrhœal arthritis in which hetero- and autovaccines, administered for a long period and with most careful attention to detail, failed to effect improvement. A surgeon was requisitioned, who, by dilatation of the urethra under an anæsthetic, removed the focus of infection and allowed the vaccine treatment to exert its influence.

Pollock and Harrison (1912) found that vaccine treatment had no effect in cutting short the acute stages of urethritis, but that excellent results followed its use in arthritis. They believed that stock vaccine made from a number of different strains is practically as good as autogenous vaccine. With regard to the relative value of vaccines prepared from old and from recent cultures, they did not think that sufficient work had been done on this subject to enable any conclusions to be drawn.

Rohrbach (1912) and Dorn (1912) obtained excellent results with "Arthigon" in arthritis cases.

Hagen (1912), on an experience of 59 cases treated with Reiter's vaccine or with "Arthigon," obtained no particular results in arthritis, but got a striking improvement in epididymitis cases. He considered that vaccine therapy often caused a hyperæmia of the spermatic cord.

Simon (1912) got good results with vaccine in epididymitis and prostatitis, but saw no evidence of benefit in acute urethritis cases.

Fromme (1912) had good results with Reiter's vaccine and with "Arthigon" in epididymitis and arthritis (80 per cent of recoveries). Cases of pyosalpinx also were often greatly benefited. Out of 45 cases treated with Reiter's vaccine 10 were cured, 19 markedly improved and 6 slightly improved, but 10 cases did not appear to derive any benefit. With "Arthigon" he got a subjective improvement in 70 per cent of 75 cases of pyosalpinx, 11 cured, 29 considerably improved, 20 slightly improved and 15 unaffected. He got better results where, instead of a quick rise as advocated by Bruck, he increased the doses slowly, commencing with 0.5 c.c. and rising with increments of 0.1 to 0.25 c.c. about every four days until a dose of 7 c.c. was reached. He emphasised the necessity for care with regard to dosage, recommending that it should not be administered unless the temperature was normal. When a general reaction was produced by the vaccine after the second injection of the same dose, he reduced the subsequent dose slightly and increased the interval between the injections. In addition to vaccine he also advised local treatment such as hot air, hot douches, etc. Cases of recent Bartholinitis, gonorrhœa of the external genitals and the cervix were, in his opinion, not benefited by vaccine, and the disease in some cases spread to the appendages during the treatment. He was unable to understand how Schmitt (1912) got a cure with Reiter's vaccine in 12 out of 24 cases of cervical gonorrhœa.

Dembska (1912) obtained satisfactory results with vaccine in gonorrhœa of the uterine appendages.

Zieler (1912) states that systemic gonorrhœal infection is the main field for vaccine therapy, and that this treatment had given us a weapon wherewith to attack these conditions which were hitherto beyond our reach. It acts by stimulating the production of antibodies or other defensive substances. It is extremely important, however, not to neglect local treatment at the same time. Acute or subacute infections respond better to vaccine therapy than the chronic or torpid forms of systemic gonorrhœa.

Nicoll and Wilson (1912) described a case of general gonococcal infection in a male child aged two and a half years. The condition arose from a urethritis. Excellent results were obtained by the administration of polyvalent gonococcal vaccine in doses of 100, rising to 200 millions.

Cholzow (1912) describes a case of gonococcus septicæmia, proved by blood culture. An abscess was found in the prostate and evacuated. The patient was transfused with saline and an autogenous gonococcal vaccine was injected subcutaneously. Five injections of the vaccine were given before final recovery in the fourth week.

Kreissl (1912) considered that vaccine was valuable in systemic gonococcal infections, if given in conjunction with local measures at the focus of the disease. He advocates the evacuation of purulent joint exudates.

Boehm (1912) also recommended vaccine for gonococcal complications.

Duncan, Menzer, Knoll, Recio, Guggisberg, and Müller (1912) have all written papers in favour of vaccine therapy in gonorrhœa.

Lehr (1912) reported on a case of gonococcal pyelitis, in which he administered three doses of 50 millions, 75 millions and 100 millions of gonococcal vaccine at intervals of six days. As this treatment had apparently no effect, he washed out the pelvis of the kidney several times with a weak solution of silver nitrate, and brought about a complete and rapid recovery.

Slingenberg (1912) used polyvalent gonococcal vaccine in the vulvo-vaginitis of girls, and in women with gonococcal tubes and ovaries. This treatment was very successful in a number of cases. He recommends caution, however, as some of his patients reacted with great intensity to even minute doses. On the other hand, some had only a slight reaction with large doses.

Morrow and Bridgman (1912) published an account of the treatment of 300 cases of gonorrhœa in girls. The majority of the cases were subacute or chronic, and the majority of them had a cervicitis.

They considered that douches were not only useless, but worse than useless, regardless of what antiseptic was used in the douche. Instillations of argyrol were not much better than douches. Silver nitrate (25 per cent) applied to the cervix and 10 per cent to the vagina once a week proved best. Gonococcus vaccine when used alone did not prove entirely satisfactory, since there seemed to be a general tendency to a recurrence after the vaccine was discontinued. On the other hand, it gave most excellent results in all cases with involvement of the joints.

The results of various treatments in the 300 cases was as follows :—

Treatment Used.	No. of Cases.	Time required for the Gonococci to disappear.		
		Least Months.	Greatest Months.	Average Months.
Four per cent silver nitrate	120	2	24	11
Vaccine alone	17	1	5	4
Vaccine plus ichthyol	101	1	8	4
Vaccine plus 25 per cent AgNO ₃ . . .	30	17 to 30 days	4	2
Twenty-five per cent AgNO ₃	32	10 to 30 days	4	2

They conclude, that for cases in which a speculum can be used, silver nitrate (25 per cent to cervix and 10 per cent to vagina) should be applied twice weekly, and that this treatment is enhanced by the administration of gonococcal vaccine. For little girls and in virgins with innocent infections the use of gonococcal vaccine gave the best results, but the condition was somewhat liable to recur when the vaccine was stopped. Vaccine is of the greatest use in cases with joint complications, and hence it is almost invaluable.

Alderson (1912) had a remarkable success by injecting gonococcal vaccine in a case of acute gonorrhœal conjunctivitis.

Vandegrift (1912) succeeded in curing a case of gonococcal chorioiditis with vaccine alone. The patient had a localised chorio-retinitis, attended by severe hyalitis. He had

also chronic prostatitis. The expressed prostatic secretion showed large numbers of staphylococci and gonococci, and the complement-fixation test was strongly positive to gonorrhœa.

A mixed vaccine (Parke Davis) containing 100 million gonococci and 125 million staphylococci per c.c. was given in doses of $\frac{1}{4}$ c.c., $\frac{3}{4}$ c.c., 1 c.c., 1 c.c., 1 c.c., and 2 c.c. during a period of two and a half months. Both the gonococci and staphylococci disappeared in about five weeks. The eye condition improved gradually and cleared up completely in four months, and the complement-fixation test became negative at the end of the sixth month.

M'Donagh and Klein (1912) state that it is far more important to use a vaccine recently made from an original culture or first subculture of gonococci than to lay stress upon the vaccine being autogenous. They tried three methods of vaccine therapy.

- (1) Ordinary vaccine injected intramuscularly or subcutaneously.
- (2) Autolysed vaccines injected intravenously.
- (3) Sensitised vaccines injected intramuscularly or subcutaneously.

The disadvantages of the first method were a marked negative phase and toxic symptoms after a long course of treatment. By using the second method the negative phase was practically negligible, but the toxic symptoms could not be avoided. Sensitised vaccines overcame all these difficulties, provided a human anti-gonococcal serum was employed in the sensitising.

Bruck (1912) maintained that the estimation of the opsonic index during vaccine treatment was superfluous. He pointed out that the leucocytes naturally ingested the gonococci, but that the latter were not damaged in any way by this active phagocytosis. In fact, the leucocytes and the germs lived together in a state of symbiosis. It therefore appeared to him illogical to base the administration of the vaccine upon the opsonic index, when it was well known that this power of the leucocytes already existed naturally to a maximum degree. He agreed with the majority of observers that vaccine was valuable in certain gonorrhœal complications such as arthritis, epididymitis and affections of the uterine appendages. (No effect of course was obtained in old fibrosed epididymitis nodules, in ankylosed joints, or in gynæcological cases with mixed infection.) He thought that it was of doubtful value in the vulvo-vaginitis of little girls, and he had never seen any curative effect from vaccine in the case of simple urethral infections.

In administering vaccine he believed that it was good practice to produce a temperature reaction, and for this reason advised against giving too small an initial dose. Autogenous vaccines were better than heterogenous, but the difficulty of providing the former was solved practically by the production of a polyvalent vaccine such as "Arthigon." He commenced with 0.5 c.c. of this vaccine (intramuscular). If the temperature rose 1° C. or over he waited three or four days and then repeated the same dose. On the other hand, if the reaction was small the dose was doubled. As a rule the course of treatment consisted as follows:—0.5 c.c., 1 c.c., 1.5 c.c., 2 c.c., etc. More than five or six injections were seldom necessary, and doses higher than 2 c.c. were seldom injected. He considered that it was inadvisable to give vaccine in cases of arthritis and epididymitis accompanied with fever. In such patients the temperature was usually reduced to normal in two days by rest in bed and moist dressings, and thereafter the vaccine therapy was commenced.

In his opinion the good effect of the vaccine depended on a reaction analogous to the effect of tuberculin in tubercular foci. He believed with Schindler that this reaction caused the gonococci in the encysted foci to disintegrate in large numbers, and so antigen and then antibody was produced. This did not occur, however, in gonorrhœa of the mucous membrane, because the disintegrated products of the germs were removed too rapidly through the medium of the pus and urine, hence the lack of good results with vaccine in cases of simple gonococcal urethritis.

Tudehope (1913) treated a case of gonococcal pyæmia with gonococcal vaccine, commencing with 50 millions and increasing to 100, 200 and 400 millions. The patient

recovered. There was a decided reaction with the last dose, with rise of temperature, headache, nausea and vomiting.

Jack (1913) tried vaccine therapy in 6 cases of gonococcal vulvo-vaginitis. He stated that his results were not very encouraging. Two cases lasted two and a half months, and 1 case over three months. The remaining 3 cases were still uncured after two, five and over five months.

Fitzgibbon (1913) treated 6 cases of gonorrhœal vaginitis with gonococcal vaccine. Three were children, one an adult with a recent infection, and two adults with a chronic infection. Four of the cases cleared up uninterruptedly from the beginning of the treatment; the other two improved, but relapsed again. One of these finally became cured. The sixth case became clear of inflammation and discharge for three weeks, then relapsed. He maintained that in children the infection was often purely gonococcal, and in these the vaccine might be sufficient. He advised local treatment chiefly for cleanliness, but it was also necessary and important in chronic cases where there was a mixed infection. He considered that in order to be effective the vaccine should be made from cultures grown fresh from the human host, but they need not be autogenous. He gave doses somewhat over 5 millions.

Neu (1913) was sceptical with regard to the value of vaccine, and could not understand why it should be of value in old chronic cases and not in recent acute conditions. He concluded from an extended trial of gonococcal vaccine in the gynæcological clinic at Heidelberg that no vaccine had yet been produced which was effective in the treatment of chronic gonorrhœa in the female.

Hauser (1913) with vaccine therapy in 18 female gonorrhœa patients obtained excellent results in 29.4 per cent and satisfactory results in 52.9 per cent. Thus 82.3 per cent of his patients with gonorrhœal lesions in the ovaries or tubes were materially benefited. His results were also good in chronic cervical gonorrhœa and in cases with cystitis. He noticed in all cases of long-standing adnexal swellings an improvement in the subjective symptoms and in the clinical well-being. An objective improvement, however, was only noticeable in early cases. He stated that vaccine was far from being absolutely harmless, and that it should be used only under constant medical control. It was contra-indicated during the period of menstruation.

Klause (1913) summarised his opinions with regard to gonococcal vaccine as follows :—

(1) The vaccine deteriorated on keeping, and should not be used after it was three months old.

(2) The best results were obtained by giving increasing doses in four- to five-day intervals. First dose 5 to 10 millions, and the next dose should always be about double the preceding dose. Usually it was sufficient to increase up to 100 or 200 millions.

(3) A little fever was no contra-indication to vaccine therapy.

(4) Gonococcal vaccine possessed no prophylactic value.

(5) Its therapeutic value was greatest in cases of epididymitis and arthritis. In these complications the success was almost invariably good and often surprisingly good. It had not the same definite effect, however, in adnexal and cervical affections of women, or in the parenchymatous prostatitis of man. The results were very doubtful in folliculitis, and it had no effect in cases of urethritis, catarrhal prostatitis and proctitis.

(6) In relatively recent cases he found little or no effect, but better results were obtained with older cases.

(7) Lasting bad effects were not found with gonococcal vaccine. The untoward effects were very trivial, considering the advantages. He had no lasting bad effects in several patients to whom he gave an initial dose of 1000 millions.

(8) A trial with gonococcal vaccine was indicated in all cases.

(9) In the course of a gonorrhœal affection the existence of hidden foci could be brought to light by the injection of a dose of vaccine.

Semenow (1913) stated that polyvalent gonococcal vaccine was a specific remedy

in the treatment of chronic gonorrhœal arthritis. It stopped the pain in the joints and gradually reduced the temperature to normal. A temperature of 37° to 38° C. was no contra-indication to the giving of the vaccine. It sometimes increased the discharge from the urethra, and diarrhœa was a very occasional disagreeable secondary effect. It was not necessary to estimate the opsonic index. For cure it was necessary to give some eight to twenty injections in six to sixteen weeks. It should be given every four to six days at first, but as the doses got larger, every six to seven days. The gonococci in the urethral secretion disappeared only very seldom under the influence of the polyvalent vaccine alone.

Saynisch (1913) recommended for epididymitis a combination of vaccine treatment ("Arthigon") and local applications of ichthyol on cotton-wool compresses. Ichthyol was applied the first day. Next day 0.5 c.c. of "Arthigon" was injected intravenously, but if the temperature was higher than 38° C. he only gave 0.1 c.c. Four intravenous injections were usually sufficient. Good results were obtained by this combined treatment in 20 cases. When any fibrosis remained he injected 10 per cent fibrolysin.

Finkelstein and Gerschun (1913) used a polyvalent gonococcal vaccine, obtained from cultures grown on blood or ascitic agar. The vaccine was made up with saline and heated to 60° for one hour. They commenced with a dose of half a million germs, increasing at intervals of six or seven days up to 50 millions. Rapid curative results were obtained in cases with arthritis and epididymitis. They also stated that in ordinary urethral gonorrhœa the gonococci disappeared quickly from the discharge.

Roucaÿrol (1913) reported on the cure by vaccine therapy of an old case of gonorrhœal urethritis which was in the habit of recurring during attacks of influenza.

Mittendorf (1913) wrote on the treatment of gonorrhœal ophthalmia with gonococcus vaccines, and Armstrong (1913) reported on a case of gonorrhœal warts of the face successfully treated by vaccine.

Erlacher, Fossati, Marotto, Menzer, Brandweiner, Brandweiner and Hoch (1913), all reported favourably on the vaccine treatment of gonorrhœa.

Heymann and Moos (1913) got good results with vaccine in the gonorrhœa of women and girls, and Johnson (1913) also found it to be valuable in female gonorrhœa.

Runge (1913) considered that gonococcal vaccine was valuable in gynæcological cases of gonorrhœa such as salpingitis.

Kyrle and Mucha (1913) found that "Arthigon" (commercial gonococcal vaccine) was good, in that it rapidly reduced the swelling in epididymitis.

Asch (1913) did not find that "Arthigon" was of much value in cases of urethral gonorrhœa, though in individual cases it undoubtedly was followed by beneficial results.

Bardach (1913) was very pleased with the effect of "Arthigon" in 22 cases. The best results were obtained in arthritis and epididymitis cases. There was also some success in prostatitis. He administered this vaccine intravenously, and thought that large doses were better than small ones. In two of his cases the injection was followed by high fever lasting for two to three days. In his opinion the vaccine had no effect in destroying the gonococci situated in the urethral mucous membrane. In two of his cases epididymitis occurred during the treatment, and one case of single epididymitis developed into a double infection, but on the whole no bad effects were produced by the treatment.

Frank (1913) was impressed with the value of "Arthigon" both as a therapeutic and as a diagnostic agent. Kreiblick (1913) claimed good results with intravenous "Arthigon" in 13 cases of iritis. He gave doses up to 2.5 c.c. and got several severe reactions, with languor, thirst, giddiness, tenesmus and pain in the loins.

Habermann (1914) watched the effect of "Arthigon" in 32 cases. He did not give more than five injections to each. In 2 cases of primary urethritis it had no beneficial effect; one developed prostatitis and the other developed a double epididymitis. One case of acute prostatitis showed numerous gonococci after the third injection. Better results were obtained in 4 cases of chronic prostatitis. In one of these the urine cleared

up and the discharge had nearly dried up after the second injection. In 1 case of arthritis and 1 case of epididymitis he observed an extension of the disease during treatment. He pointed out that Rost, Fockler and Menzer also noticed the occurrence of complications during treatment with "Arthigon," and on the whole he was not highly impressed with the value of this vaccine, and he concluded that "Arthigon" given intravenously was no better as a therapeutic and diagnostic agent than the ordinary gonococcal vaccines given hypodermically. Animal experiments would appear to have shown that intravenous administration produced a more rapid production of antibody, and the reactions produced by intravenous injection were certainly greater than by the hypodermic route. But in his experience clinically he did not agree that a severe reaction was followed by a corresponding therapeutic success. He considered that the dose given by the intravenous route should be small and increased with great care, according to the preceding reaction.

Bruck and Sommer (1913) treated 19 cases of gonorrhœa with "Arthigon" given intravenously. They began with doses of 0.1 c.c., increasing gradually at three or four days' intervals, according to the reaction produced by the last injection. Rarely more than six injections were given, the last dose reaching 0.6 c.c. Their observations led them to believe that the greater the reaction the greater the therapeutic effect, and especially good results were obtained in those cases which showed a double rise of temperature after the vaccine. They considered that the intravenous administration gave better results than obtained by the intramuscular route. The injections were not dangerous, and fever was no contra-indication. Three cases of prostatitis with anterior and posterior urethritis, and treated locally as well as with "Arthigon," cleared up and the gonococci permanently disappeared. In 5 cases treated with "Arthigon" alone the gonococci disappeared permanently after one to four injections. Three cases did not clear up, and they attributed the failure in cases of pure urethritis to the supposition that the antigen did not find enough "receptors" in the system to provoke a reaction, and consequently the formation of antibody was slight. In a few cases complications occurred during treatment. In a case of infantile vulvo-vaginitis, gonococci were still present after six weeks. Their results agreed more or less with those published by other observers, and were summed up as follows:—

Excellent results in epididymitis and arthritis.

Moderate results in prostatitis, vulvo-vaginitis and cervical gonorrhœa.

Negative results as a rule in primary urethritis, but in a few of the latter cases it might effect a cure without local treatment.

Roth, Klinger and Oppenheim (1913) reported failures with "Arthigon." The latter observer saw a double epididymitis supervene during treatment with "Arthigon" and "Gonargin," and attributed this to the focal reaction stimulating an anti-peristalsis in the vas.

Freund (1913) stated that "Arthigon" was a specific remedy in gonorrhœa. It was quite harmless. It was especially valuable in epididymitis, and was generally recognised by all as a superior remedy. It quickly relieved the pain and cut short the disease. It was also valuable in cases of acute arthritis, and sometimes also in acute prostatitis.

Tedesco (1913) reported on 7 cases of gonococcal arthritis treated with "Arthigon" administered intramuscularly, and he concluded that it was an excellent remedy.

Frühwald (1913) used "Arthigon" intravenously in gonorrhœa and noticed considerable reactions.

With regard to "Gonargin" (a commercial gonococcal vaccine) Schumacher (1913) got good results by intravenous injection in 3 cases (2 epididymitis). The intravenous administration produced in his hands intense reactions with fever and malaise. The reaction was much more mild by the intramuscular route, and he did not find that a more rapid therapeutic effect was attained by intravenous injection. He considered that there was no reason for preferring this method to intramuscular administration.

Heden (1913) used "Gonargin" in the treatment of gonococcal arthritis, and considered that it was superior to other curative agents.

Sensitised Gonococcal Vaccine.—Cruveilhier (1913) employed gonococcal vaccine which was sensitised according to the method devised by Professor Besredka (1911). He maintained that in cases of epididymitis treated with this type of vaccine the pain usually disappeared in twelve to twenty-four hours after the first injection. Next day the patient had no difficulty in standing or walking, and the symptoms of local inflammation disappeared with the pain. Each patient received two or three injections at intervals of forty-eight hours, and no relapses were reported. Excellent results were obtained in utero-adnexal complications. After the second or third injection the abdomen recovered its suppleness and ceased to be painful on palpation, also the swelling at the site of the tubes disappeared. It seemed, moreover, to relieve cases of metro-salpingitis of long standing. In acute arthritis, good results were obtained in every case. They were usually cured after four or five injections. One case of chronic arthritis was greatly improved after nine injections given over a period of twenty-five days, but it was not completely cured.

The best effects were obtained in gonorrhœal complications, but he also had good results in acute and even in chronic urethritis. Most cases cleared up in four weeks without any complications.

The vaccine was sensitised with the serum of a goat which had previously been immunised by intravenous injections of gonococci. In certain cases where the dead vaccine failed, he got excellent results with a living sensitised vaccine. Besredka (1911) proved that living sensitised vaccine was more efficient than the dead.

Cruveilhier maintained that it was unnecessary to use autogenous vaccine. His good results were obtained with stock material several months old. The sensitised vaccine did not produce any severe general reaction. Sometimes it caused a slight rise of temperature, and sometimes some redness and pain at the site of injection, which never lasted longer than forty-eight hours.

Dopter and Pauron (1913) reported that they had obtained excellent results by adopting Cruveilhier's method of treating gonorrhœal rheumatism with sensitised gonococcal vaccine. In one case the first injection produced a marked general reaction, but on the following day the pain and swelling had greatly diminished. After the second injection the patient was cured, having become normal in five days. The cures were startling, and superior to those obtained by any other treatment. Old-standing chronic cases required longer treatment. Similar excellent results were obtained in cases of epididymitis. In twenty-four hours after the first injection the pain disappeared and the swelling diminished. After three or four days the patient was able to walk about freely, and was quickly cured.

Broughton-Alcock (1913) treated 26 cases of uncomplicated acute gonorrhœal urethral discharges with sensitised gonococcal vaccine, but was unable to notice any definite curative effect. None of the patients, however, developed any extension of the infection or any complication. He gave varying doses of the germ, in some cases up to 3000 millions. He also treated 25 complicated cases, comprising epididymitis, arthritis, tendinitis, etc. The epididymitis cases gave the most satisfactory results. Most patients were free from pain after the first injection; sometimes, however, three were required. It took about three weeks to reduce the nodular filtration to the size of a pea. He had two cases of relapse. In cases of acute arthritis the pain often disappeared within forty-eight hours, and the exudations disappeared in three days. The cure persisted when the patients were seen one month later. Cases of subacute tendinitis without exudation required one to three weeks of injection treatment with the vaccine. In this author's opinion the value of the sensitised vaccine is due to the large doses which can be given. He started with a dose of 500 millions and increased to 3000 millions without any very severe local or general reaction. He sometimes repeated the doses within seventy-two hours. He was unable to find that living sensitised gonococci were any better than dead sensitised vaccines.

McDonagh and Klein (1913) stated that the complement-fixation test could be used for regulating vaccine treatment in gonorrhœa. They divided vaccine treatment into three methods:—

- (1) Subcutaneous injections of ordinary vaccine.
- (2) Intravenous injections of autolysed gonococci.
- (3) Subcutaneous or intramuscular injections of sensitised vaccine.

They found that the vaccine sensitised with a human anti-gonococcus serum was far superior to a vaccine sensitised with immune horse serum. They maintained that vaccines were often necessary in addition to other local or general treatment in order to obtain a cure. The injection of a potent vaccine was able to promote a new artificial kind of immunity, more effectual than that already established naturally in the injected individual.

The Non-Toxic Vaccine of Nicolle and Blaizot, "Dmego."—Nicolle and Blaizot (1913) introduced a new gonococcal vaccine under the name of "Dmego," for which they claimed the special properties of stability and non-toxicity.

According to these authors the disadvantage of gonococcal vaccine was its toxicity, and even Besredka's method of sensitising had failed to abolish this defect. They claimed to have reduced the toxicity in a marked degree by growing the gonococci in a special medium containing meat broth 100 c.c., urea 0.4 grams, glucose 2 grams, phosphate of ammonia 0.5 grams, and agar 1.5 grams. This medium was tubed 5 c.c. in each, and finally 0.5 c.c. of rabbit serum was added. The growths were emulsified in 0.7 per cent sodium fluoride and repeatedly washed and centrifuged in this solution, which, they claimed, prevented autolysis and lessened the toxicity.

Further, to this vaccine they added a Gram-positive coccus frequently associated with the gonococcus in the proportion of one part of gonococcus to nine parts of the "syncoccus." The initial dose of this vaccine "Dmego" was 0.5 c.c. containing 250 millions, *i.e.* 25 million gonococci and 225 millions of the "syncocci." The dose of vaccine is diluted with 1.5 c.c. of saline and injected deeply into the muscles. The authors claim a definite cure in acute cases of gonorrhœa in less than fifteen days, and gonorrhœal ophthalmia in the newly-born was often cured by one injection.

Remlinger (1913) reported favourably on the above vaccine.

Bar and Lequex (1913) also got good results with it in 4 cases of salpingitis in women, and in a case of purulent ophthalmia in an infant four days old. They claimed that the latter case was cured by one injection. The four salpingitis cases were cured by four, three, three and seven injections respectively.

Sauvage (1913) reported that "Dmego" had no effect on a case of acute gonococcal vulvo-vaginitis in a little girl complicated with tubal infection and peritonitis. This case was operated upon and gonococci demonstrated in the tubes.

Further reports on "Dmego" are reported below; *vide* (1914).

Gonorrhœal Phylacogen.—"Phylacogen" was a trade name of bacterial products prepared according to the directions of Dr. A. F. Schäfer (California). They consisted of a filtrate of staphylococcus albus, aureus and citreus, also staphylococcus pyogenes, *B. pyocyaneus*, diplococcus pneumoniae, *B. typhosus*, *B. coli*, streptococcus rheumaticus, streptococcus erysipelas and gonococcus. Being a filtrate, it was more of the nature of a germ autolysate than a vaccine.

L. W. Harrison (1913) tried gonococcal "Phylacogen" in 16 cases of gonorrhœa, including one of arthritis, and 10 cases of epididymitis. He found that pain was produced at the site of injection, and considerable fever with headache and even rigors were produced when it was administered intravenously. It seemed to be successful in relieving the pain in the case of arthritis, and appeared to have hastened the recovery. He did not find, however, that it had any therapeutic value in the other 15 cases, except that it appeared to relieve the pain in the epididymitis cases, more especially after the large doses. He thought that this may have been due to the febrile reaction produced. He also tested the antigenic power of the "Phylacogen" in the complement-fixation test,

and found that it did not act as a good antigen, being inferior to an ordinary emulsion of gonococci.

McCall (1913) treated 30 cases of chronic rheumatism, rheumatoid arthritis and chronic gonorrhœa with "Phylacogen," and got very good results except in 2 cases. He obtained good results in a case of chronic gonorrhœa by giving five doses at two days' intervals. The first dose consisted of 5 c.c. and was increased to 7 c.c.

Digested Bacterial Extracts.—Hirschfelder (1913) introduced a digested gonococcus solution as a therapeutic agent in gonorrhœa. A suspension of gonococci was dissolved at 38° C. by adding 0.2 per cent pancreatin solution in 2 per cent sodium bicarbonate. The ferment was allowed to act for fifteen minutes, and then the solution was acidulated with hydrochloric acid to stop the action of the enzyme. Finally the solution was filtered through a Pasteur filter. The filtrate was administered intravenously in doses of 5 c.c., and the dose could even be increased with safety to 50 c.c. It was apt, however, to cause malaise and fever. In acute and chronic urethritis in the male the results obtained were not very satisfactory. He considered that the antibody produced in the blood was unable to get at the gonococci in the urethra. Good results, however, were obtained in females, and especially in systemic infections where the joints or the epididymides were involved.

Troisfontaines (1914) treated 3 cases of acute epididymitis with "Dmego." The pain and swelling disappeared rapidly after two injections, but the discharge was not influenced. Two cases of arthritis were cured by three injections.

Broussegoutte (1914) cured 3 cases with "Dmego" given intravenously, and combined with local treatment. In one of the cases (acute orchitis) the pain disappeared quickly after the vaccine, but the discharge continued. Only two injections, however, were given in this case.

Fromaget (1914) gave two injections of "Dmego" in a case of ophthalmia. The case relapsed and had to be treated with silver nitrate.

Leuret (1914) described 3 cases: (1) Urethritis (two months), cured after three injections of "Dmego"; (2) arthritis (four months' duration), cured after four injections; and (3) arthritis (three months' duration), cured in nine days after four injections.

Mauriac (1914) got good results with "Dmego" in 1 case of arthritis, but it had apparently no effect on 2 cases of urethritis.

Fieux (1914) tested "Dmego" in 2 cases of acute exacerbation in chronic salpingitis and was satisfied that it was beneficial. It failed, however, in a case of ophthalmia neonatorum.

Wansey Bayley (1914) found that some cases were benefited by "Dmego," but he was not much impressed with its merits.

Donaldson (1914) tried "Dmego" in 4 cases—two females with vaginal discharge, and two males with chronic gleet. It did not show any marked beneficial result, and gonococci continued to be present after nine injections.

Taussig (1914) came to the conclusion that gonococcal vaccine was useless in the treatment of gonorrhœa of the mucous membranes. He also obtained little benefit from treatment by the lactic acid bacillus.

Habermann (1914) treated 19 cases of gonorrhœa with "Arthigon" with moderate results. Several cases relapsed, and in some complications supervened during the treatment.

Brahns (1914) got some good results with "Arthigon."

Leslenyi and Winternitz (1914) also used "Arthigon" in 36 cases in females. He did not find it of any definite value in urethritis, vaginitis or cervicitis, and it did not prevent complications, as in one case Bartholinitis supervened. Out of 18 cases with adnexal gonorrhœa the vaccine had no effect in 9. Four showed a subjective improvement, and in 5 cases there was definite clinical improvement as well. The cases which were markedly improved by the vaccine did not react to the injections any more vigorously than the others. He also treated two cases of arthritis with excellent results.

Moos (1914) got good results with intravenous injections of "Arthigon" in the gonorrhœa of women.

Bruck (1914) also found this vaccine a valuable adjunct in the treatment of gonorrhœa.

Cholzoff and Graminitzky, Ilinsky, Strong, Jungano, Szily, Becker, Arnold and Holzel, and Boeters (1914), all obtained a certain amount of success in the treatment of gonorrhœa with gonococcal vaccines.

Henry (1914) reported on 9 cases of gonorrhœa in women treated with vaccine; 5 were cured or benefited, but it had no effect in the remaining 4 cases.

Hamburger (1914) failed to get any benefit from vaccine therapy in the gonorrhœa of children.

Strebel (1914) recorded a cure of gonorrhœal keratitis after injections of gonococcal vaccine.

Sémionov (1914) got excellent results with vaccine in cases of chronic gonococcal arthritis.

Block (1914) did not get such good results with vaccines as recorded by other observers. He, however, had no bad effects as a rule in 40 cases treated with subcutaneous or intramuscular injections. He stated that only a few instances of complications had been published in which the preceding vaccine therapy had been blamed. He administered the vaccine in a few of his cases by intravenous injection, and the results surpassed his highest expectations. The reaction was very severe, but the rapid subsidence of gonococcal arthritis, epididymitis, prostatitis, etc., impressed him as to the therapeutic value of this mode of administration. The idea occurred to him that the curative effect might be due to the intense reaction rather than to any specific influence. In consequence he treated three other patients suffering from unusually severe gonorrhœal arthritis with intramuscular injections of anti-typhoid vaccine. The febrile reaction produced by this non-specific vaccine was followed by a prompt subsidence of the joint symptoms, and finally produced a complete cure. Block did not venture to generalise from these three cases, but he thought that they helped to confirm Gerhardt's statements that intercurrent infectious diseases had a favourable influence on the course of gonorrhœa. Such experiments cast a certain amount of doubt on the specific nature of certain reactions, and sustained, in his opinion, the old theory of revulsion and counter-irritation, and it suggested an explanation for the benefit reported from tuberculin in various supposedly non-tuberculous diseases.

Chiari (1914) reviewed 470 articles published on gonorrhœal arthritis during the previous ten years, and he tabulated 433 cases in which vaccine therapy was applied with autogenous or commercial vaccine. Only 42 cases were uninfluenced; 32 patients were improved, and 367 were cured. He stated that the progress in the previous decade had been such that arthritis cases could now be cured by vaccine therapy combined with physical measures, and marked improvement could be brought about in even apparently desperate cases.

Unpleasant Effects from Vaccines.—Leslenyi and Winternitz (1914) recorded certain untoward effects arising as the result of treatment with gonococcal vaccine. These consisted of pains in the head and body, sometimes vomiting, and in one case repeated nose bleeding. In one case of arthritis they had to stop vaccines on account of marked symptoms of heart weakness.

Arnold and Holzel (1914) cited Lewiniski's case of acute cardiac insufficiency developing after an intravenous injection of gonococci. Heart disease was not known to be present in this case. On the other hand, Luithlen (1915) reported on a case of gonococcal endocarditis successfully treated with intravenous injections of gonococcal vaccine. Culver (1917) had a case of gonorrhœa with mitral regurgitation, who became cyanotic, with feeble, irregular pulse lasting from ten to fifteen minutes. These symptoms occurred about three hours after the injection of the vaccine. Culver stated that many such instances have been reported, and advises care where there is cardiac disease. He

states further that vaccines do not seem to affect the kidneys and do not produce albuminuria.

Fockler (1914) reported epileptiform seizures in two patients after intravenous injections of vaccine. One of these, however, was ascertained to have had meningitis, and was the subject of fits afterwards. The other was apparently healthy. Fischer in one instance noted cerebral symptoms which passed off in twenty-four hours. Culver (1917) produced delirium in three patients after a large dose of *B. coli* vaccine. This disappeared in twenty-four hours, but they had diarrhoea afterwards for two or three days, and they were very weak and prostrated. Bateau had a patient who suffered from intense pain in both forearms and wrists after an injection of gonococcal vaccine. There was no apparent swelling, however.

Dorn reported on a case in which after the second injection of gonococcal vaccine a considerable albuminuria resulted. This, however, cleared up soon afterwards.

Cruveilhier (1914) recorded further successes in the treatment of gonorrhoea with his sensitised vaccines.

Roux (1914) agreed with Mayoral and Grande in that a pure gonococcal vaccine was good in systemic gonorrhoea; for example, in arthritis and epididymitis cases. It was not so good, however, in urethral conditions, because in this locality the gonococcus was associated with other organisms. It was therefore necessary to give a mixed vaccine for urethral gonorrhoea. He agreed with Nicolle and Blaisot that a Gram-positive coccus was very frequently associated with the gonococcus.

Solari (1915) reported good results with vaccines in streptococcus and gonococcus affections.

Froloff (1915) obtained excellent effects with vaccine in gonorrhoeal arthritis.

Ribes and Lawrence (1915) had success with vaccine therapy in cases of gonorrhoeal iritis.

Stümpke (1915) found gonococcal vaccine of value for both the diagnosis and treatment of gonorrhoeal affections.

Perez Grande (1915) had good results with polyvalent vaccine in the gonorrhoea of both males and females.

Gaujoux (1915) found it to be of value in gonorrhoea connected with gynaecology and obstetrics.

Brett (1915) recorded 33 cases of acute urethral gonorrhoea treated with commercial gonococcal vaccine (B. W. & Co.). The first dose consisted of 200 millions injected into the buttock; forty-eight hours later he injected a second dose of 1000 millions, and two to three days later another 1000 millions. The patients were kept at rest in bed on milk diet, and the urethra was washed out with weak potassium permanganate three to four times daily. The vaccine usually caused a temperature of about 99.9° F., with slight headache and temporary increased discharge next day. After the discharge cleared the patient was allowed up, but had no exercise. These cases were cured in an average of thirteen and a half days. No case was regarded as cured till the discharge had ceased for four or five days, so that the disease on the average only lasted nine days.

He considered that his success was due to the large doses of vaccine administered, and maintained that most of the failures in vaccine therapy were due to small dosage and too long intervals between the injections.

Madden (1915) found gonococcal vaccine very disappointing in pure gonococcal infections of the urinary tract, and considered that it was contra-indicated in acute cases. In chronic urethral gonorrhoea pure autogenous gonococcal vaccines were rarely of much value, and stock gonococcal vaccines were of little use. In these chronic cases secondary organisms such as staphylococci, short bacilli, diphtheroids and diplococci of various sizes were very common. A mixed vaccine made of these organisms produced a rapid improvement in chronic gonorrhoea both clinically and bacteriologically. He advocated that local treatment should always be combined with the vaccine treatment.

Warden (1915) pointed out that the gonococcus undergoes lysis very rapidly in watery saline emulsions, so that most gonococcal vaccines are really autolysates of the gonococcus and are very toxic. He thought therefore that injections would produce only antibodies towards the toxic products of lysis, and that this would account for the relief of pain in the vaccine treatment of gonococcal arthritis. Apart from the relief of pain due to neutralisation of the toxic autolysate he did not consider that the injections produced any marked production of anti-substance towards the gonococci themselves. He was able to separate from gonococcal autolysates a fatty portion and a nitrogenous portion. The fatty or lipid portion was less toxic than the nitrogenous part, and it was even more valuable antigenically. By employing the lipid moiety suspended in alcohol as an antigen in the complement-fixation test he got more positive tests than with the nitrogenous portion. The lipid moiety was non-toxic for normal persons and animals, even when given intravenously in large doses. He treated cases of gonorrhœa with subcutaneous injections of this lipid gonococcal substance, and in all cases, whether acute, chronic, simple or uncomplicated, he obtained marked improvement. Some were undoubtedly cured. The injections produced a slight local reaction of reddening and swelling, and sometimes a general reaction.

Sullivan, E. A., and Spaulding, E. R. (1916) state that vaccine therapy, even in children, in whom it is supposed to give the best results, has not in their experience produced the results that are claimed for it. They rely therefore more on the actual treatment of the infected tissues themselves.

Hyman (1916) treated 25 cases of gonorrhœa with Nicolle and Blaizot's vaccine "Dmagon." He gave a total of 3000 millions in six to eight injections. In acute cases the vaccine was given every day or every other day, and in chronic cases every two to four days. No local treatment was employed. Twenty-eight per cent of the cases were cured. The best results were obtained in joint cases and in chronic prostatitis, but it had little effect in acute urethritis.

Non-specific Vaccine Therapy, Anaphylaxis, etc.—Müller and Weiss (1916) became convinced that the efficacy of the vaccine therapy of gonorrhœa depended mainly on the febrile reaction which it induced. The benefit was more apparent the more intense the febrile reaction, and the benefit, as a rule, was apparent before there could have been time for antibodies to have developed. These and other considerations suggested to them that similar benefit might be obtained from injection of any non-specific alien albumin. They reported the results of treatment on this basis in 40 cases; milk was used in some and sodium nucleinate in others, and was injected intramuscularly. The therapeutic effect fully equalled and usually surpassed that of intravenous vaccine therapy. Gonorrhœal epididymitis, arthritis, prostatitis or urethritis promptly retrogressed, with rapid subsidence of pain and other disturbances. They regarded the results as a brilliant therapeutic success. The temperatures produced by their injections amounted to 104.7° F.

Smith (1916) used injections of normal horse serum in order to produce anaphylactic shock, and the results obtained corresponded favourably with those produced by anti-gonococcic serum. He found that the more severe the reactions produced, such as fever, urticaria, joint pains, etc., the better were the results; and when no allergic symptoms developed after the injections, no effect was obtained on the disease. He got good curative results where anaphylaxis was produced without a temperature reaction, so the effect could not be attributed to the high fever. He finally admits that this anaphylactic treatment is hazardous.

Jobling and Petersen (1916) used proteose injections in typhoid-immune rabbits, and found a decided increase in the antibody titre, which is explained by a selective stimulation of the hæmopoietic system by a non-specific substance.

Walther, Hildebrand, Engelhardt and Rolly and Meltzer conclude that high temperatures artificially produced have a favourable influence on any established infection, but that, on the other hand, cold seems to retard the formation of immune bodies.

Jobling and Petersen, however, believe that there are factors at work other than fever, and assert that intravenous injections of foreign proteins cause a fluctuation in the ferment-anti-ferment balance of the serum, as well as changes in the coagulation mechanism and the opsonic-complement properties, all of which tend towards a condition favourable for recovery from infection.

Miller and Lusk (1916) found striking therapeutic results in arthritis due to other infections than gonorrhœal, as well as in gonorrhœal patients, by the intravenous injection of typhoid vaccine. The streptococcus and other organisms causing arthritis are not especially sensitive to heat, so the improvement must have been due to other factors than the fever produced by the injections.

Culver (1917) studied the subject of non-specific inoculations very carefully.

(a) He injected thirteen gonorrhœal subjects intravenously with 100 million gonococci every four or five days. Fever was produced in twenty minutes to one hour, and a transient headache. The average temperature after three hours was 103.9° F.; this passed away in twelve hours. Occasionally severe pain was produced in the affected parts. The severity of the reaction usually decreased after repeated injections. There was usually a transient leucocytosis soon after the injections, just before or during the first symptoms of fever; then there occurred a marked leucopenia towards the end of the fever, followed by a gradually developing leucocytosis. This reached its maximum in five to seven hours, remained moderately high for twenty-four to thirty hours, and became again normal in about forty-eight hours. The average leucocytosis produced was 33,000 per c.mm. The highest he recorded was 55,000 per c.mm., and the lowest 22,000 per c.mm. The increase was due entirely to the polymorphonuclear type.

(b) Fifteen cases of gonorrhœa were injected intravenously with 100 million meningococci, and exactly the same results were produced as with the gonococci, except that more than half developed a more or less severe herpes of the lips and mucous membranes of the mouth. This herpes came on forty-eight hours after the injection, and remained for four to seven days..

(c) Seven cases were treated with *B. coli* vaccine intravenously, with again the same results, except that the symptoms of fever, etc., produced were more severe. Too severe a reaction was produced by 100 millions, so it was found necessary to reduce the dose to about 25 millions.

According to Culver, the therapeutic results obtained in these three series of cases were the same. He found, however, that good results were not obtained unless there was a definite fever, followed by a leucocytosis after the injections.

In the above series of cases 24 had arthritis as well as urethritis. The most striking results were produced in the acute and subacute cases. The chronic cases seemed to respond more slowly to treatment, but did not show the same tendency to relapse as the acute cases. All but two of the 24 were completely cured, or showed decided improvement. The length of treatment varied from two days to one month. Three patients with very acute arthritis were able to walk out of hospital in three days after one injection. Two cases, however (both acute), were refractory, in spite of the fact that they reacted as well as the others, showing both fever and leucocytosis.

Twelve patients had acute epididymitis, and invariably the pain subsided in them after the first injection. Usually not more than two injections were necessary, and indeed in most instances one was sufficient to produce a cure. The swelling began to subside within twenty-four hours after the injection, and the patient usually left hospital on the fifth or sixth day. The injections, however, were not prophylactic against the development of new complications, as occasionally during treatment the other testicle became affected, or even a joint became involved.

The effect on the urethral discharge was decidedly variable. In some it was more profuse for two or three days after the injection, and then suddenly subsided entirely; in others there was a marked decrease following each injection; while some of the very

chronic discharges were not influenced at all. The gonococci decreased in number and usually disappeared after four to six injections.

Culver (1917), in a later paper, maintained that primary and secondary proteose preparations, when injected intravenously, stimulated antibody production for specific organisms in gonococcal arthritis in a manner not to be distinguished from that produced by the injection of the specific organisms themselves. In cases of gonococcal arthritis an injection of proteose caused either no change or else a decrease in the antibody content of the serum within the first twenty-four hours. The first injection usually caused the greatest clinical benefit, and produced an increase in the quantity of lytic substances, even during the first twenty-four hours following an injection, so that the subjective and objective improvement in favourable cases could not be attributed to an increase in antibodies alone. He stated that it was difficult to determine how much therapeutic influence, if any, was brought about by the leucocyte increase.

Haab (1918) states that the greatest advance in ophthalmic therapeutics of recent years is the treatment of gonorrhœa of the eye by subcutaneous injections of 1 c.c. of a typhoid bacillus vaccine containing 5 millions of germs. The injection is repeated next day or later. This method was advocated in 1917 by Szily and Sternberg, who reported the complete cure of 68 cases in adults in a few days. Haab tried it with considerable scepticism on a girl of five with violent inflammation of the eye. In two days the eye was free of secretions and cocci. In his five other cases the results were not so promptly apparent, but the cure was complete in all in two or three weeks, and injury to the cornea was averted. More than two injections of the vaccine can be given if necessary. There is a brief reaction, then in two or three days the inflammation in the eye subsides and the cocci disappear. He mentions that genital gonorrhœa in the young and old does not seem to be affected by the typhoid vaccine.

Trossarello (1920) has given parenteral injections of milk in the treatment of 45 cases of gonococcus infection and in 15 cases of venereal bubo. Fever develops about two or three hours after the injection, and this allows out-patient treatment, as the patients are able to reach home before the fever commences. No benefit was apparent in cases of urethritis, prostatitis, epididymitis or arthritis, but in ovarian and tubal gonorrhœa marked improvement was produced. All were benefited, some by a single injection. The results in his 20 cases of adnexal gonorrhœa surpassed, in his opinion, those obtained with specific vaccines or antiserums; the pain subsided promptly, even before any objective improvement was apparent. The results obtained in his 15 cases of venereal bubo were equally encouraging, and he thinks that early treatment of this nature would abort these lesions. He injected into the buttocks 5 or 10 c.c. of ordinary milk at intervals of 3 or 4 days, and gave a total of five injections. The febrile reaction appears to be the main therapeutic factor, and the best results were noted in the patients that presented the strongest reactions.

More Recent Literature on Vaccine Therapy of Gonorrhœa.—Lamb (1917) reported on 500 cases of acute gonorrhœa treated with vaccines. The vaccine used, called "Staph-gon," consisted of 20 million gonococci and 50 million staphylococci per c.c. The dosage was as follows:—

1st day	$\frac{1}{4}$ c.c. = 5 million gonococci.		
3rd "	$\frac{1}{2}$ c.c. = 10	,	"
5th "	$2\frac{1}{2}$ c.c. = 50	"	"
9th "	"	"	"
13th "	"	"	"
16th "	"	"	"

Weak potassium permanganate irrigations were also used. The discharge almost invariably ceased by the sixteenth day.

Out of 50 cases on the above treatment, 37, or 74 per cent, were discharged after an

average duration of twenty-two days; the other 13 cases (26 per cent) were complicated with prostatitis, and one had epididymitis. The vaccine also proved valuable in a case with a para-urethral abscess.

He had excellent results in four cases with acute arthritis. All recovered. Five hundred cases of acute gonorrhœa were treated with the following dosage of vaccine :—

1st day	50 million gonococci.
3rd "	100 " "
6th "	100 " "
9th "	" " "
12th "	" " "
15th "	" " "

The vaccine was then stopped for ten days, after which a second course of six injections of 100 millions was given on the twenty-fifth, twenty-eighth, thirty-first, thirty-fourth, thirty-seventh, and fortieth days respectively. Many cases required the first course only. He gave a final dose of 100 million gonococci as a test of cure. If this resulted in no discharge, the patient was considered clear.

Results obtained :—

Number of uncomplicated cases	278	} Average days in hospital, 43 days.
Number of complicated cases	222	

Of the uncomplicated cases 157, or 60 per cent, were cured in an average of nineteen days; average duration of the remaining 121 was fifty-five days.

The statistics of the complicated cases were as follows :—

Epididymitis	101 cases; average days required to cure, 38.
Prostatitis	94 " " " " 60.
Arthritis	10 " " " " 50.
Acute prostatitis and epididymitis	17 " " " " 86.
Average duration of all complicated cases = 52 days.					
Average duration of all uncomplicated cases = 35 days.					

Number of cases which relapsed four to six months after treatment was only two; that is, less than 1 per cent.

Kidd (1917) appears to believe that vaccines are useless, but he gives no statistics on the matter.

Haworth (1918) got excellent results with sensitised vaccines in gonorrhœal arthritis, using fairly large doses. He reported 16 cures out of 17. He sensitised his vaccine by using a commercial anti-serum. The serum and gonococcal emulsion were mixed and incubated for twenty-four hours at 37° C. After centrifugalisation the supernatant serum was removed, and replaced by saline.

In chronic or complicated cases he recommended the following course: first day, 25 millions; second day, 50 millions; third day, 100 millions; fifth day, 150 millions; seventh day, 200 millions; then increasing by 50 millions every third day up to 550 millions; and then increasing by the same amount every fifth day.

A second series of cases was tried on the following course :—

1st day	100 million gonococci
5th "	200 " "
9th "	400 " "
13th "	600 " "
17th "	800 " "
21st "	1000 " "
25th "	1200 " "

and increasing by 200 millions every fourth day up to a maximum of 2000 millions.

He used strains less than four months old, and claimed absence of reaction, except rarely.

Shera (1918) found that the vaccine was unstable and that the strains varied in potency, thereby confirming Torrey's observations. He considers that vaccine is valuable in both acute and chronic cases of gonorrhœa.

Le Moignic, Sezary and Demonchy (1918) used an anti-gonococcal vaccine prepared by the methods used in the preparation of the anti-typhoid lipo-vaccine of Le Moignic and Pinoy. Eighteen-hour-old cultures of the gonococcus are incorporated with the oils used in the preparation of the anti-typhoid lipo-vaccine. The vaccine contains about 5 milligrams of dead culture, or about 12,500 millions of gonococci in a cubic centimetre. The commencing dose is 0.5 c.c. of the vaccine. This is increased gradually, and two or three injections are given during the week. The vaccine is injected into the subcutaneous tissues of the flank, and there is but little local reaction.

Sézary (1919) states that large dosage is an important factor in effecting a cure. Thus he employs gonococcal lipo-vaccine with excellent results. Four to five c.c. of the vaccine, containing in all 60 to 80,000 millions, must be given. This material is given in four to six injections.

Janet (1918) found gonococcal vaccine beneficial in gonorrhœal rheumatism, and he thinks that the vaccine may yet serve in local treatment of the primary gonorrhœal process, when the technique is better worked out. Cathelin stated that the vaccine was only useful in the complications of gonorrhœa.

Baril and Creuzé (1919) obtained a cure in from 12 to 25 days in 95 per cent of 300 cases of acute and chronic gonorrhœa, including 50 cases in women. They ascribe this success to the use of a polyvalent gonococcal vaccine in addition to the local treatment.

Pineo and Baillie (1919) reported on the successful treatment of gonorrhœa with pus vaccines.

Demonchy (1919) obtained satisfactory results in the treatment of gonorrhœal urethritis with injections of unheated vaccine combined with potassium permanganate. Repeated doses of 5000 to 10,000 million cocci (0.0025 to 0.005 gramme of moist culture) caused a cure sooner than if urethral injections of permanganate were given alone. If, however, larger doses, 80,000 to 200,000 millions (0.04 to 0.1 gramme), be given, the curative effect is much more marked. Autogenous vaccines are better than stock. With a first attack of gonorrhœa, the injection of a dose of about 150,000 millions of cocci is usually followed within forty-eight hours by the transformation of a purulent into a mucous discharge, and a complete cure results within three to six days.

Boas and Thomsen (1919) tabulated their results in the treatment of recent uncomplicated gonorrhœa in men with a vaccine made from several strains of gonococci grown on ascitic agar.

Twenty-four-hour cultures were used, emulsified in 0.9 per cent saline. In 202 cases not treated with the vaccine, 45 per cent developed complications, but only 19 per cent of 126 cases treated with the vaccine developed complications. The results were in reality more favourable than this, as in 7 of the 23 complication cases of the latter group a vaccine had been used which was proved later to be defective. The complications in the vaccine cases were very mild; there was a prostatitis only in 3, while in the non-vaccine cases prostatitis formed half of the 90 complication cases.

Van den Branden (1919) states that the best results are always obtained with vaccines of recent production. He got good results in 57 acute cases of epididymitis. Twenty-two days was the average stay in hospital.

Fraser and Duncan (1920) believe that vaccine given intravenously is the best mode of administration. They got as good results with T.A.B. vaccine as with gonococcus vaccine. The largest dose of gonococcus vaccine given was 2000 millions.

Lorenzo (1920) reports a case of gonococcal arthritis of the temporo-maxillary joint which improved under three weeks of vaccine therapy.

Messerschmidt and Walther (1920) found that an autogenous vaccine containing all the types of secondary organisms found in the prostatic secretion exerted a favourable influence on post-gonorrhœal prostatitis without the aid of further therapeutic measures.

Bloch and Hébert (1920) reported a case of febrile gonococœmia of pseudo-malarial type with arthralgia and an eruption which simulated the picture of meningo-cocœmia but showed no response to anti-meningococcus serum. A vaccine was then prepared from a diplococcus cultivated from the blood, and immediate improvement in the above symptoms followed its subcutaneous injection. The vaccine, however, had no effect on the urethritis and epididymitis of the chronic gonorrhœa in this case.

Geraghty (1921) states that gonorrhœal vaccine or any of its modifications are utterly useless in the treatment of acute or chronic gonorrhœal urethritis, and that an occasional good effect in epididymitis and arthritis is not the result of specific action. The author is inclined to doubt if Geraghty has ever read the literature on the subject, or if he has used gonococcal vaccine much. His statements are certainly so dogmatic that they would appear to be only justified by divine inspiration. Geraghty further states that in acute gonorrhœal epididymitis the intra-muscular use of horse serum is followed in 50 per cent of cases by a rapid subsidence of pain and tenderness. He recommends the injection of 5 to 15 c.c. deep into the lumbar or gluteal muscles.

Frassi (1921) used gonococcal vaccine alone in 9 cases of vulvo-vaginitis in little girls with or without complications, and he records a complete recovery in each case. Four to eleven injections were given, and the subsidence of the vaginal discharge was more rapid than under any other form of treatment. A stock gonococcal vaccine was used.

Frassi (1921) also wrote a monograph on vaccine and serotherapy in gonorrhœa, which won the Paravicini prize. His paper is based on 146 cases of gonococcal epididymitis and 23 cases of joint complications treated with gonococcal vaccine, as well as other material. He gives the conclusions of other observers all over the world. There is a bibliography of five pages. Everything, he says, tends to confirm the great value of anti-gonococcal vaccine and serum in the diagnosis and treatment of the surgical complications of gonorrhœa, especially when used in connection with surgical measures. Antibodies are found in the blood from the first days of the gonococcus infection. The gonococcus passes early into the blood, even when the infection seems a purely local process. Chill, trauma and over-exertion may favour a systemic spread of the infection. A general reaction to a diagnostic injection of vaccine is not specific or typical, but a focal reaction is common in joint complications, salpingitis, and epididymitis. A negative reaction, however, is not conclusive, as the dose of vaccine may have been too small, or there may be a mixed infection, or the process may be so old that it is incapable of reactivation either by the skin, the intradermal or the ophthalmo-reaction.

The complement-deviation test seems to be absolutely specific when positive, but is not conclusive when negative. Agglutination and precipitation tests are uncertain. Auto-serotherapy is giving good results, and may be given a trial in suitable cases. During treatment with serum and vaccines new complications seldom develop; the pain and swelling in a joint may be relieved by a single injection, but the complete cure usually requires from four to eight weeks.

Sézary (1921) prefers doses of vaccine which just give a mild febrile reaction. In 9 of his 150 cases the orchitis or arthritis vanished the day after the first injection. The vaccine has to be continued, however, to prevent reinfection from the gonococci still lurking in the tissues. Three days is usually a long enough interval between the injections. He uses a gonococcal lipo-vaccine, commencing with 0.5 c.c., and follows up with 1 c.c. and then 2 c.c.

Richard (1921) gives a long review of the recent literature which confirms the efficacy of antigenococcus vaccine and serum against the complications of gonorrhœa. He states, however, that the gonococci in the urethra are seldom affected by this treatment.

Buschke and Langer (1922) state that gonococcal foci are usually inaccessible to

direct medication, and urge the necessity for perfecting vaccine therapy as apparently the only way to root out the disease in many cases.

Wulff (1922) analyses the results of vaccine treatment of 100 cases of infection of the urinary tract in Rovsing's hospital in Copenhagen in the period 1911-20. Cases of gonorrhœa were not included, and in the overwhelming majority the coliform group was responsible for the disease. The author classifies his cases according as they were characterised by (1) acute febrile exacerbations or relapses, or (2) by a comparatively mild and chronic course. There were 43 in the first class, 32 in the second. In the first class 21 patients were cured, and 16 improved. In the second class 16 were cured, and 10 improved. In a third class, containing 17 cases of pyelitis with calculi, there were 8 in which the calculi could not be removed. Of the remaining 9 patients, one was cured and 7 were improved. The author, who is greatly impressed by the importance of autogenous vaccine treatment, and who has come to the conclusion that spontaneous recovery is exceedingly rare in this class of case, notes that in about 80 per cent recovery or definite improvement can be achieved by vaccines. In the remaining 20 per cent vaccines produced no benefit, for some unknown reason. The most important effect of vaccine treatment is the cessation of relapses or exacerbations, and in many cases freedom from such exacerbations may be maintained for several years. The author recommends an initial dosage of 10 to 30 million germs, and in some cases he has increased the dose to 10,000 million germs.

Gonorrhœa is very frequently a mixed infection wherein staphylococci, *B. coli*, etc., play a part as well as the gonococcus, and Wulff's article is mentioned here in order to emphasise the importance of administering in such cases a mixed vaccine containing the secondary organisms. There are so many species of the latter that an autogenous vaccine is advisable where possible.

SUMMARY AND CONCLUSIONS BY THE AUTHOR

An analysis of the above references shows that out of about 250 articles dealing directly with the effect of gonococcal vaccine in gonorrhœa, only five, or 2 per cent, state that it is of no value as a therapeutic agent. On the other hand, 245, or 98 per cent, agree that the vaccine produces beneficial and curative results. Many of the authors state that the vaccine is beneficial, without going into details as to the forms of gonorrhœa in which the best effects are obtained. Others deal only with certain complications of the disease, such as arthritis or epididymitis, etc. A few give definite opinions as to its comparative value in the various forms and complications in the male and female. Further analysis therefore brings out the following statistics of opinion:—

Phase of the Disease.	Number of Articles.	Opinion on Vaccine Therapy.
Arthritis	68	66 = Excellent results. 2 = No effect.
Epididymitis	35	35 = Very valuable.
Prostatitis	14	11 = Good results (especially in chronic follicular). 3 = No effect.
Spermato-cystitis	1	1 = Good (curative).
Cystitis	1	1 = No effect.
Pyelitis	1	1 = No effect.
Proctitis	1	1 = No result.
Systemic gonorrhœa (septicæmia)	5	5 = Excellent.
Pyæmia	1	1 = Excellent.
Warts on face	1	1 = Curative.
Keratitis	1	1 = Curative.
Conjunctivitis	5	4 = Curative. 1 = No effect.
Iritis	5	5 = Curative.
Choroiditis	1	1 = Curative.
Acute urethritis	33	17 = Good results. 16 = Little or no effect.
Chronic urethritis	12	12 = Good results.
The disease in general	35	34 = Good results. 1 = No effect.
Complications in general	4	4 = Good results.
Female gonorrhœa in general	6	5 = Good results. 1 = No effect.
Vulvo-vaginitis in children	20	16 = Good results. 4 = No results.
Bartholinitis	1	1 = No effect.
Cervical gonorrhœa	6	4 = Good results. 2 = No effect.
Gynæcological cases (salpingitis and ovaritis)	15	14 = Good results. 1 = No effect.

There can be no doubt whatsoever, therefore, that, according to those observers who have taken the trouble to write upon the subject, gonococcal vaccine is of therapeutic value in practically every phase of gonorrhœa. The best results have been obtained in certain complications such as arthritis, epididymitis and salpingitis. It is very valuable in complicated cases in general. It is valuable in chronic urethritis and prostatitis, and has least effect on acute urethritis. With regard to females, it is valuable in vulvo-vaginitis, cervicitis, and especially valuable in adnexal affections such as salpingitis and ovaritis.

No one who has studied the literature can possibly deny the accuracy of these conclusions.

With regard to the best variety of gonococcal vaccine and the best mode of administration, it is more difficult to draw deductions from the literature. It would appear, however, that autogenous vaccines are best, but that stock polyvalent vaccines are almost as good. Some observers believe that vaccines made from recent strains are better than those made from old subcultured strains, and that vaccines deteriorate on keeping and should not be used after three months. Certain authors, however, got the best results with vaccines made from old strains, but no one so far has dared to assert that vaccine improves the longer it is kept, like whisky or brandy. The author is inclined to believe that very excellent vaccines can be obtained from old and long-subcultured strains of gonococci. Some assert that they become less toxic thereby, and this should be a good point, as larger doses of the vaccine could be given. Further, is it not just possible that a vaccine might become less toxic by being kept for a very long time? and might it not therefore

be better than a new vaccine, because larger doses could be given without toxic effects? Experiments (see Immunity) have shown that the endo-toxin is of very doubtful value in the stimulation of immunity. At any rate it is obvious from the literature that much more research requires to be carried out before we can come to any definite conclusions on these points.

With regard to dosage, it would appear that the large doses are best, provided the toxic symptoms and the negative phase are not too severe. The whole trend of vaccine therapy has been in the direction of finding some method of increasing the dose, so as to produce a corresponding increase in the amount of immune body in the system. For this reason "Dmagon" was produced and praised because it was non-toxic, and could be given safely in large doses. The virtue of sensitised vaccine appears also to lie in its reduced toxicity, whereby increased doses can be administered. The favourable opinion on sensitised vaccine, however, is not entirely unanimous. Swift and Kinsella (1916) found that unsensitised vaccine proved to be better than the sensitised in producing antibodies in the case of the streptococcus in rabbit experiments. White and Graham (1909) maintained that the infective power of tubercle bacilli for rabbits was greatly increased by sensitisation with normal rabbit serum.

Kakchi (1915) has shown by immunising experiments upon animals with sensitised and non-sensitised vaccines that the toxicity of the former is less than that of the latter. A sensitised vaccine is a vaccine treated with its corresponding immune serum for six to twelve hours at room temperature. The idea is to hasten the process of immunisation by performing the first stage *in vitro*. It would appear, however, that the chief advantage of a sensitised vaccine is that it is less toxic, and so larger doses can be given.

The author has already referred to the tendency in recent years to treat diseases such as gonorrhœal rheumatism, etc., with injections of foreign or non-specific proteins such as typhoid bacilli. The idea is that benefit and increased immunity are produced by "anaphylaxis" or "protein shock." The author is against this non-specific treatment; because if there is any virtue in "protein shock," why not produce it with a specific vaccine? The shock will be produced if a sufficient dose is given, and at the same time specific anti-substances will be formed as well. It would appear from the literature that injections of typhoid vaccine certainly do produce benefit in gonococcal arthritis. This may possibly be due to the fact that the chemical composition of typhoid germs resembles that of the gonococcus. At any rate, both germs are Gram-negative and both are easily soluble in weak alkali. Thus it may be that anti-substances against the one may act to some extent as antibodies against the other. The idea is put forward as a possible explanation of the beneficial effects of some non-specific vaccines. Further observations and researches by the author on vaccines and "detoxicated vaccines" are given in the next chapter.

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CHAPTER XXXI

THE AUTHOR'S RESEARCHES ON THE DETOXICATION OF VACCINES

THE writer has during the past four years devoted so much time and research to this subject that it is impossible to go into the full details of the matter in this chapter.

Those who are interested should consult the original papers already published, *vide* Thomson (1919, 1921, 1922), Lees (1919 and 1921), Corbett and Osmond (1920), Fraser and Duncan (1921), Jenkins, Heywood, Corsar Sturrock, and Langley (1921).

During the past two years the author has investigated the literature bearing on this subject very carefully, and hopes in due course to bring out a book dealing with the problems of detoxication, immunity and the biochemistry of germs in full detail.

It may be stated with some truth that the science of vaccine therapy and the science of preparing vaccines has been more or less at a standstill for the past ten years.

Every one feels that there is some virtue in vaccine therapy. Remarkable results are frequently obtained, and anti-typhoid inoculation has been a great success. Mingling with this success, however, and the hope that a great future for medical treatment lies in this direction, there has been much disappointment, discouragement and failure. We seem still to be groping in the dark. We are in a rut, trying in vain to find the true path to the ultimate secret of eminent success in the production of a powerful immunity towards the seeds of various diseases.

It would almost seem that some observers have been going backwards instead of forwards, since attempts have been made to explain the effects of vaccine therapy as due to "protein shock," temperature reactions, anaphylaxis, etc. Such explanations seem to ignore the fact that specific anti-substances are produced by living animals against bacteria and other foreign proteins, when the latter are injected.

This fact, proved beyond all doubt by thousands of experiments, must never be lost sight of. It is the dominant fact of the science. Those who waver in this belief need only remind themselves that a serum highly surcharged with a specific anti-substance is sold as a commercial product, which has been used by hundreds of scientists every day for the last ten years. (It is used in the Wassermann Test.) This commercial product is rabbits' serum containing a large amount of anti-substance towards sheep's red cells. It is known as amboceptor, and so powerful is the anti-substance present that it is capable of dissolving sheep-cells even when the serum is diluted 2000 times with saline. Some sera, indeed, retain this solvent power even at dilution of 1 in 20,000.

If the serum of a given human being contained so much bacteriolytic substance against the gonococcus that it could even when diluted 2000 times still dissolve the gonococcus, what a powerful immunity that person would have towards gonorrhœa! An immunity of such a potency towards a given germ would render the individual absolutely incapable of contracting the disease. Indeed, $\frac{1}{100}$ th part of such an immunity would render him quite safe.

If it is possible to produce artificially in a rabbit a quantity of anti-substance to a foreign protein so potent as just described above, why should it not be possible to

develop artificially a similar quantity of potent anti-substance in a human being towards the foreign protein of a given germ?

It has already been proved by thousands of experiments, and it is admitted by scientists generally, that when an emulsion of dead germs is inoculated into a human being, specific anti-substances towards these germs are developed in the human serum. It is also admitted, however, that these anti-substances are developed in very small amounts, so small indeed that in many cases it is almost impossible to detect them, even by the most delicate blood-tests. Perhaps the most delicate chemical test known is the complement-fixation reaction, and in many instances it fails to detect the presence of these antibodies after several injections of bacteria, *i.e.* of vaccine.

Why is so much anti-substance produced against sheep's corpuscles by the injected rabbit, and why is so little produced against bacteria when the latter are injected? Both are foreign proteins, so why should the results be so discrepant? In the author's opinion the answer is very simple and obvious.

To get good sheep-cell amboceptor or anti-substance produced in a rabbit, one injects as a rule about 5 c.c. of solid sheep red cells, or roughly 5 grammes of the wet foreign protein. A rabbit weighs on the average 2000 grammes, so that $\frac{1}{400}$ th part of its weight of foreign protein is injected.

A man weighs on the average 64,000 grammes, or roughly thirty times the weight of a rabbit, so that a comparable dose of foreign protein injected into a man would be 150 grammes of the wet substance.

In the case of vaccine therapy let us see what doses are actually injected in our attempts to produce immunity. With the ordinary toxic vaccines, the total quantity injected in several doses varies according to the toxicity of the vaccine from about 500 to 5000 millions. In some cases it is much less in amount.

Now, germs are so small that 5000 millions represent about $\frac{1}{250}$ th of a gram of the wet substance, or about $\frac{1}{9,600,000}$ th part of the weight of the man. This is a dose twenty-four thousand times smaller than the quantity of sheep-cells injected into a rabbit. Can one wonder, therefore, that the germ anti-substance can often not be detected after such an extremely small dose?

With the author's detoxicated vaccines the total dosage of germs varies from 20,000 millions to 100,000 million organisms, or at least twenty times greater than in the case of the toxic vaccines. In many cases it is more than 100 times greater. If we take the average total injected as 100,000 millions, this represents about $\frac{1}{125}$ th of a c.c. of the wet germ substance, or $\frac{1}{800,000}$ th part of the body weight of the man. This is 2000 times smaller than the dose of foreign protein given to the rabbit, as mentioned above.

Although, therefore, a dose of 100,000 million germs may seem enormous—and it is enormous in comparison with the dose of ordinary toxic vaccines—yet in mass it is less than $\frac{1}{10}$ th of a cubic centimetre, and that is a very small amount to inject into a comparatively large animal such as a man.

Reasoning on these lines it would appear that a very powerful or highly potent immunity towards bacteria will not be obtained until we are able to inject doses of germ substance amounting to 1 c.c. or more of the semi-solid wet protein. With such doses of the foreign protein, a very appreciable amount of bacteriolytic anti-substance should be produced, large enough in quantity to be easily detected in the serum and easily measured.

If the large amount of hæmolysin produced in a rabbit by injections of sheep's corpuscles is due to the massive doses, then much less hæmolysin should be produced by inoculations with extremely tiny doses.

The above arguments appear to be rational and logical, and the following experiments were carried out in order to confirm them or otherwise.

The points to be settled by experiment are as follows :—

(1) Will extremely small inoculations of sheep-cells into a rabbit, comparable with the exceedingly small doses of ordinary toxic vaccines, produce an appreciable or measurable amount of hæmolsin in the rabbit's serum ?

(2) Will inoculations of sheep-cells into a rabbit, comparable in amount to doses of 100,000 millions detoxicated vaccine, produce larger amounts of hæmolsin ?

(3) Are inoculations of sheep-cells into a rabbit, in amounts comparable to doses of 1 c.c. of germ substance into a man, capable of producing a potent hæmolytic serum ?

These experiments were carried out in the following manner :—

(1) Rabbit "A" was injected with six minute doses of sheep-cells, comparable in size to human inoculations of 100 millions, 200 millions, 500 millions, 1000 millions, 1500 millions and 2000 millions of germs respectively. That is to say, the dosage was comparable in size to the doses of ordinary toxic vaccines given to a man.

(2) Rabbit "B" was injected with six doses of sheep-cells comparable in size to the following doses of detoxicated vaccine in a man, viz. 5000 millions, 10,000 millions, 25,000 millions, 50,000 millions, 75,000 millions, and 100,000 millions of germs respectively.

(3) Rabbit "C" was inoculated with six doses of sheep-cells comparable in size with six doses of 1 c.c. of germ substance into a man, i.e. doses equal to 1,000,000 million germs. Taking the rabbit as $\frac{1}{20}$ th the weight of a man, the actual dose it received amounted to $\frac{1}{20}$ th of a c.c. of sheep-cells, or a total of $\frac{6}{20}$ ths or $\frac{3}{10}$ ths of a c.c. in all.

The amboceptor content or hæmolytic power of the serum of each of these rabbits was estimated against sheep-cells before and after each inoculation, and the results were graphed in the accompanying manner.



FIG. 19.

The results of these inoculation experiments, as clearly shown in Fig. 19, were as follows :—

(1) The hæmolytic titre of the serum of rabbit A was tested every few days after each small inoculation, but the results were negative. Extremely small inoculations of sheep-cells therefore produce no detectable amount of immune substance.

(2) Rabbit B showed that with doses comparable to 50,000 million germs and upwards in a man, the hæmolytic titre rose in marked manner, so that the serum became potent even in a dilution of 1 in 100.

(3) The experiment in the case of Rabbit C showed clearly that with doses comparable to one billion germs in a man the immune substance rose to such an extent that this serum showed a hæmolytic titre of 1 in 480.

These experiments, therefore, give conclusive support to the view that the amount of antibody produced becomes greater and greater when larger and larger doses of the foreign protein are injected.

Large doses of germ material will therefore when injected induce the formation of large quantities of anti-substance against that particular germ protein.

Arguments which have been brought forward against Detoxicated Vaccines.—One of the first criticisms brought forward against detoxicated vaccine was that a non-toxic substance produced no reaction when injected, and hence could produce no anti-substance. This criticism is, however, entirely wrong. For example, sheep-cells are non-toxic to a rabbit, yet they induce most successful anti-substance formation. Sheep-cells are 2000 times less toxic than the least toxic vaccine so far ever produced, so that if we detoxicated germs 1000 times more efficiently than at present they should still be capable of producing potent anti-substance when injected. The second criticism brought forward is almost equally groundless and erroneous, but it is more difficult to disprove. The contention is that it is bad to remove the toxins, because they are antigenic and stimulate the formation of antitoxins. Furthermore, the toxins produce reactions, and these reactions are essential for successful antibody formation.

To go into the full details of the defence against these contentions would take up much time and space, but it will be sufficient to state them shortly as follows :—

- (1) Antibodies are only produced against highly complex proteins.
- (2) Antibodies are not produced against the simple disintegration products of proteins such as amino-acids, etc.
- (3) The toxic substances removed from germs by the author's process are very simple nitrogenous protein products, since they are soluble in absolute alcohol. This is sufficient to show that these simple toxic products are of little value in immunity.
- (4) The toxic products do not act antigenically when used in the complement-fixation test.
- (5) These simple toxins are not to be compared with the true exotoxins, such as the toxins of diphtheria and tetanus bacilli. These latter true toxins are precipitated by alcohol. They are highly complex protein substances like snake venoms, and antitoxins are produced against them.
- (6) Very few germs contain true highly complex protein toxins.
- (7) The simple toxins are very poisonous and harmful to the system, and should not be injected when they are of no antigenic value.
- (8) When we aim at getting immunity towards a germ we wish to get an anti-substance which will kill the bacterium rather than an anti-substance which will only neutralise its poison. For example, if we are defending ourselves against venomous snakes, it is surely better to kill the snakes outright rather than to attempt to render them harmless by removing their venom sacs only.
- (9) A reaction does not *per se* produce any antibody. For example, intense reactions can be produced by injecting absolute alcohol or other such irritants under the skin, but no anti-substances are produced against these irritants.

The third criticism is that the detoxication process may alter the nature of the germ proteins so much as to destroy their specific antigenic value. This is the most reasonable criticism of the three.

It has been proved experimentally, however, that the detoxication process does not destroy the specific antigenic value of the germs. The detoxicated germ substance still remains a good antigen when used in the complement-fixation test. Moreover, sheep-cells when put through the same process are still capable of producing hemolysins when injected into a rabbit; *vide* Balls and Korns (1918). Tissue cells when put through the process are capable of producing specific cytolytins when injected into another species of animal; *vide* Kolmer (1917).

It would appear, therefore, that the criticisms which have been launched against detoxicated vaccines are not supported by experimental facts, and the arguments used are erroneous.

On the other hand, the superiority of the immunising power of large doses as compared with infinitesimal doses is a fact beyond dispute. In vaccine therapy, however, we cannot get from the infinitesimal dose to the large dose without detoxication. Clinical observation and trial has already given ample proof of the superiority of the large doses of detoxicated germ proteins over the infinitesimal doses of the ordinary toxic germs.

We can see much hope in this direction. Very good results have already been attained, and extraordinary therapeutic success should be the reward when highly efficient detoxication can be carried out with a minimum of chemical alteration in the detoxicated germ substance. The author's methods to-day are much superior to his first attempts of three years ago. The detoxication is ten times more efficient, the chemical process employed is very much less drastic, and it would appear that the attainment of complete success will be achieved with further researches in this direction.

Attempts to remove the Endo-toxins, so that Massive Inoculations of Germs may be given.—The author has been working on this subject for the past five years, with the result that his attempts to remove the toxicity of germs have become gradually more and more successful.

The details of these researches up to 1922 have already been published, Thomson (1919), (1921), (1922). The problem is largely biochemical in its nature, and has involved a considerable amount of investigation into the chemistry of non-toxic as well as toxic proteins. It would be unwise and tedious to go into the full details of such chemistry in this chapter, and it is likely that the following concise and more or less simple account of the subject will be more intelligible and of more value to the reader. The two main problems to be solved are as follows:—

(1) The efficient removal of the endo-toxins from the germs to enable massive doses of vaccine to be given.

(2) To remove the poisons by a gentle process which will not so alter the germ substance as to destroy its antigenic or immunising power.

First Attempts at Detoxication.—In 1917 the author discovered that when gonococci were treated with normal sodium hydroxide they dissolved, and when this solution was then acidified with normal HCl a precipitate of the gonococcus protein was thrown down. It was discovered that this precipitate was about fifty times less toxic than the original gonococcus germs, but that the poisonous material removed resided in the acid supernatant fluid which was decanted or filtered away from the non-toxic precipitate.

Further, it was ascertained by inoculation experiments and by complement-fixation tests that the non-toxic precipitate of gonococcus protein was antigenic or immunising in nature, and gave the same specific antigenic tests as the untreated gonococcus germs themselves.

Normal NaOH is approximately a 4 per cent solution, and it was found that when the germs were dissolved with much stronger solutions, such as 15 per cent NaOH or with anti-formin, the non-toxic precipitate was still antigenic, but not quite so antigenic as when the weaker chemical was used. It was found also that temperatures from 80° C. to 100° C. rapidly destroyed the specific antigenic properties of the germ protein.

It is obvious, therefore, that in all attempts at detoxication the chemicals used should be as weak as possible, and high temperatures should be avoided.

First Improvement in the Detoxication Process.—During the two succeeding years, 1919 and 1920, the above simple process was much improved, and the whole matter became much more complicated. Thus it was found that the original non-toxic precipitate thrown down by acid was only one fraction of the germ substance, and that other non-toxic fractions resided in the toxic supernatant acid fluid.

The new process, Thomson (1921), involved the separation and recovery of a total of five non-toxic germ fractions, viz. alkali soluble, acid soluble, water soluble, alcohol soluble and chloroform soluble constituents. As each of these constituents appeared to be of antigenic or immunising value, all of them had to be recovered, and so the process

was rendered much more complicated. It was also discovered that the brown oily poisonous material which was removed was rendered less toxic by oxidation, as by treatment with ozone or hydrogen peroxide.

The non-toxic constituents were in consequence treated with these oxidising agents, but it was not found that this oxidation treatment further reduced the toxicity of the so-called non-toxic fractions to any appreciable extent. It should be pointed out here that the term "non-toxic germ fractions" is misleading, since they are only comparatively non-toxic compared with the original germ. It must be remembered that although they are fifty times less poisonous than the original germs from which they are derived, yet nevertheless the maximum dose which could be injected into a man was only $\frac{1}{125}$ th of a c.c. of the semi-wet solid precipitate substance. This is a very small dose of a foreign protein when we remember that large doses of several cubic centimetres of foreign animal proteins can be injected into man or other animals with impunity. It was obvious, therefore, that these so-called detoxicated germ fractions were still from 100 to 1000 times more poisonous than animal proteins, such as red corpuscles, animal tissues, casein, etc.

Second Improvement in the Detoxication Process.—In 1921 the author discovered that in the first step of the detoxication process some of the germs invariably escaped the solvent action of the alkali, and that when the acid was added a certain number of undissolved germs were carried down in the precipitate of the germ protein. In other words, the non-toxic precipitates of the germ substance contained a small proportion of the unaltered toxic germs themselves. The presence of the unchanged toxic bacteria, though few in number, was nevertheless responsible for a large amount of the toxic action of the so-called detoxicated vaccines. In other words, the first detoxicated vaccines were really a mixture of the non-toxic fractions, along with a small proportion of the unchanged toxic germs.

This defect was avoided by passing the solution of each germ fraction through a Chamberland filter before precipitating it. The precipitate obtained in this way after porcelain filtration was found to be ten times less toxic than before. This filtration alone, therefore, brought a tenfold increase in the dosage of the detoxicated vaccines. The maximum dose was now in the neighbourhood of 100,000 million germs or $\frac{1}{12}$ c.c. of the solid wet detoxicated germ substance, and in some instances the dosage could be worked up gradually to even 400,000 million organisms.

This success encourages the hope that still more efficient detoxication may be attained, whereby the ultimate aim of giving 1 c.c. doses of the semi-solid wet germ protein might eventually be reached.

The Mechanical Disintegration of Germs.—When germs are dissolved in very weak alkalis their specific antigenic properties, as already stated, are not impaired. It so happens, however, that certain bacteria require very strong alkali, and even anti-formin, to dissolve or disintegrate them, and such powerful chemicals are likely to damage the specific properties of the germ protein. For this reason the author has made strenuous endeavours to find some mechanical means of disintegrating the bacteria, in order, so far as is possible, to avoid the use of strong chemicals in the detoxication process. If the lipid or lipo-protein covering of the germs can be smashed, the interior and more or less liquid portion of the organism is easily dissolved in very weak alkaline fluid.

The smashing of the germs in liquid emulsions is a very difficult matter. It is their insignificance which saves them, since they measure only about $\frac{1}{30,000}$ to $\frac{1}{50,000}$ of an inch in diameter.

With the aid of a designing engineer, Mr. Macfie, the author has been able to construct a small machine which has a cutting as well as a grinding action. The first machine constructed was able to give about 20 million cuts in the emulsion per minute, and with its aid the germ emulsions can be dissolved in much weaker alkali than before. A second machine is now being constructed which will give about 500 million cuts per minute, and the emulsion will be driven against the cutting edges at the rate of two miles per minute.

There is no doubt that this machine will mark a very considerable advance in the detoxication process, and much better vaccines will be obtained by its use.

Therapeutic Results with the Latest Types of Detoxicated Vaccines. Experiments are now being carried out with vaccines which have been detoxicated with very weak chemicals through the aid of the disintegrating machine. With gonococcal vaccines prepared in this manner and filtered through porcelain filters, it is found that one can give an initial dose of about 20,000 millions, working up to 100,000 millions. Sufficient data have not yet been accumulated, but there is no doubt that the vaccines prepared in this manner are superior to those formerly produced, and it has been proved that large doses of 100,000 millions very rapidly produce a strongly positive complement-fixation reaction in the blood of normal persons.

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CHAPTER XXXII

VACCINE TREATMENT IN GONORRHŒA

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It may be said of vaccine treatment in gonorrhœa that it has caused more controversy than any other form of treatment that has been tried in attempting to obtain a cure for this disease.

Owing to the anatomical structure of the parts affected and the pathological changes that are set up during an attack of this malady, it would appear that the only reasonable common-sense method of attempting a cure would be to raise the bodily resistance towards the germ to such a pitch that it would be impossible for the gonococci to lie dormant in the cavities of the genito-urinary tract, ready to manifest themselves should an opportunity occur by anything lowering the bodily resistance. The treatment of gonorrhœa has undergone many changes during its history, and many so-called cures have proved failures. Because the original gonococcal vaccines introduced have also been tried and proved of little use, it is now difficult to get specialists to try any new vaccine at all. Many medical men, the majority of whom have never tried it, condemn gonococcal vaccine, and no later than 1917 a well-known specialist stated in a lecture that he had never had any good results from vaccine, and never expected any, or words to that effect. He had, of course, very carefully tried the vaccine treatment. Incidentally, he also condemned the use of internal medicaments, so that those sitting at the feet of Gamaliel had their line of treatment narrowed down to irrigations, with after-treatment by bougies, prostatic massage, urethroscopic examinations, and so on, but great stress was laid on the necessity of getting the patient in the very early stages. It is not proposed to condemn irrigations and to substitute for them vaccine therapy alone, for, from the point of view of cleanliness, irrigation is justified, and with what drug the irrigation is carried out matters very little, as a weak solution of any of the antiseptics commonly used will kill the superficial gonococci in a few minutes (*e.g.* potassium permanganate in a dilution of 1 in 20,000). The writer believes, however, that to use irrigations without detoxicated gonococcal vaccine is to hinder the cure and to increase the liability of the spread of the disease to the joints and the deeper parts of the genito-urinary system.

The gonococcus, like every other infecting organism, tends to produce an antibody to itself, but the rate of production of antibody is very slow in the generality of cases, and it would appear likely that in those cases which cure rapidly, the natural power of establishing resistance is very high, for undoubtedly this natural power of developing resistance helps largely in the cure. It is often noticed that if two cases, both coming under observation in the early stages, are put on identically the same irrigation treatment without vaccine, one will recover rapidly and the other persist and develop orchitis, rheumatism and all the complications possible.

It is now possible, by the complement-fixation test (which, by the way, is as freely condemned as the Wassermann reaction used to be by many people who have not only never done it themselves, but who do not even understand the principles of the test), to

determine the amount of complement-deviating antibody that is developed, and on treating the patient with vaccine the amount of complement-fixing anti-substance has been found to increase markedly. As it is admitted that the antibody which is produced by means of vaccine treatment does not differ from that produced naturally by the body, it would appear that the ideal method of treatment would be to raise the antibody as rapidly as possible, while not producing such reactions in the patient as would prevent him following his employment. The disadvantage of using the old gonococcal vaccine made from many strains of gonococci lay in the fact that, owing to the toxicity of the organism, it was not possible to give sufficiently large doses to produce resistance quickly without causing the patient discomfort or worse with the reactions produced. Thomson realised this fact from experiments in patients with ordinary vaccine, and discovered a means to detoxicate the vaccine, so that an initial dose which is freely given now, say 5000 million organisms, would in former days have been looked on with wonder, and the giver considered very reckless. So ingrained has become the fear of reactions that workers still start treatment with detoxicated vaccine with doses of 2500 millions, but as it appeared to me, the writer, that if it were the endo-toxin of the gonococcus that caused the reaction, and if, as Thomson claimed, the endo-toxin had been removed, then there is no reason why very much larger doses should not be given. The writer often commences to inject his patients with 10,000 million doses without anything but a slight local reaction. It would be very difficult to enumerate the number of gonococci in the urethra in a fresh attack of gonorrhœa, but if there are 10,000 millions in the urethra all giving out endo-toxin, then it should not be impossible for the body to take 20,000 millions with the endo-toxin removed.

By means of the complement-fixation test it has been conclusively proved that the amount of antibody or resistance developed depends on the amount of vaccine given. It is not claimed that one large dose of detoxicated vaccine will produce a cure as laid down in any standard of cure, for gonococci will still be found in the discharge; but as in tetanus the cure is produced by gradually increasing the dosage of anti-tetanic serum, so in gonorrhœa the real curative effect will be obtained only by pushing the dosage. That the bodily resistance rises rapidly cannot be doubted, as evidenced by the fact that the patients, who are nearly all engaged in heavy manual labour in mines where no facilities for irrigation exist, and who can only attend a clinic once daily for irrigations which are given in very weak dilutions, very rapidly get cured. Taking this class of patient as an example, since it has not been found in the past that he gets a rapid cure with irrigations alone, it would appear that his cure is due solely to the detoxicated vaccine. It will be objected to this that the patients have irrigations once daily, but as the leading authorities scout the idea of any usefulness from a weak dilution such as 1-10,000, except from the point of view of cleanliness, it may be claimed that it is the vaccine that brings about a cure. Even if irrigation will cure a patient, it must be under very ideal conditions as to rest, and patients that have one daily irrigation must, for the greater part of the twenty-four hours, have a fairly healthy culture of gonococci growing in the urethra. Most medical men who have treated gonorrhœa know that it will take weeks or months to clear up a case with irrigations and medicines, even under the best conditions; and although they expect to find gonococci in the discharge and in the gleet which follows, they do not doubt the efficacy of this form of treatment even after months of it, while gonococcal vaccine is condemned if it does not work a wonder in a week or two. It takes some time for the body to raise its resistance to a point where it will be efficacious in helping to cure the disease, and in no case has the complement-fixation test proved that the resistance has been naturally raised to such a high point as it has by detoxicated vaccine in the course of a few weeks. Certain cases have evidently little or no power of developing resistance naturally, as evidenced by the fact that, although coming under observation early and treated with irrigations even in concentrated solution, they develop posterior urethritis and rheumatism, necessitating rest in bed and a prolonged

course of treatment. By using detoxicated vaccine in larger doses and increasing the dosage until the patient has had a course of say 100,000 million gonococci, it is noticed that fewer cases of complications arise, and those that do occur clear up remarkably quickly if the vaccine is pushed. Two cases have recently come under observation—the first case developed orchitis due to an injury when his gonorrhœa had been under treatment for three weeks. Hot fomentations were applied to ease the pain, and the testicle became normal in six days, and did not retain the hardness usual in these cases but became soft, and to all appearances indistinguishable from the normal testicle. The second case was a feeble patient who rapidly developed traumatic orchitis. He was treated with a small dose of vaccine before the orchitis developed, and afterwards with larger doses, and recovered in seven days. Both these cases were able to carry on their work with the exception of two days in bed.

Vaccine Treatment in Gonorrhœal Rheumatism.—Although vaccine has been despised in the treatment of urethral gonorrhœa, it has not been so condemned in the treatment of gonorrhœal rheumatism. The general attitude has been that of a gynæcologist who, when recommended gonococcal detoxicated vaccine, said he did not believe in it as a cure for gonorrhœa, but he thought it might do good in gonorrhœal rheumatism. It appears to be obvious that if it will do good in gonorrhœal rheumatism it will also do good in gonorrhœa, but why medical men should favour its use in the one case and condemn it in the other it is difficult to say.

The writer found that in no case where detoxicated gonococcal vaccine has been used has rheumatism developed, and in any cases coming under observation with rheumatism the effect of the vaccine has been little short of wonderful. A case came under observation at his clinic recently suffering from syphilis, but after one injection of N.A.B. he did not present himself for a month, as he had developed rheumatism and been under treatment by his family doctor, who had ordered him to the seaside for a month. His second appearance at the clinic was due to the fact that he did not feel safe to go away without more anti-syphilitic treatment, and he mentioned that his rheumatism was very bad. Inquiries were made, and a history of gonorrhœa nine months before was elicited, but he had denied this at the first appearance, as he had been treated by his own doctor and thought himself cured, since he only had an occasional gleet in the mornings. He was examined, and no doubts existed as to his not being cured, and that the cause of his rheumatism was the gonococcus. The rheumatism appeared to be general, both legs, both arms and the shoulders being affected. Vaccine treatment was at once started, and an initial dose of 5000 million detoxicated mixed organisms was given. The relief obtained from this dose was so marked that the patient presented himself four days later to ask if he could be given another dose. The pain had largely disappeared, and his knees and ankles were much improved, but the pain and stiffness still remained in his shoulders and elbows. He was given 10,000 millions for the second dose. The treatment was continued for four weeks, with weekly doses of 10,000 millions, and the patient became able for work and wished to return to it, but as he had been ordered a month at the seaside he was allowed to proceed there. It may be said that no local treatment for the gonorrhœa was given at the time, so that it was the vaccine that cured the rheumatism. The patient was not confined to bed during the vaccine treatment.

Another case occurred in a patient who had had gonorrhœa eighteen years before, and was supposedly cured. Having indulged, however, in a severe alcoholic bout, he developed acute rheumatism, and on examination a slight gleet was discovered in which gonococci and staphylococci were found. The patient was unable to walk, and both ankle joints were swollen and painful; the knee joints and both wrists were painful, although not markedly swollen.

He was treated by rest at his home, and a few days later appeared at the clinic, where he was detained and kept in bed. An initial dose of 5000 million detoxicated secondary organisms was given, and the result was such a marked improvement that the vaccine

was pushed until a total of 60,000 million organisms was given. He was given irrigation treatment until the disappearance of all local signs, and he was discharged to continue with weekly doses of vaccine, his rheumatism being at the same time very much better. He reported to the clinic recently to say that he had never had a recurrence of the rheumatism and was perfectly well. The patient's work is such that he is exposed in all weathers, with considerable walking and kneeling.

Another similar case was treated, and improved as rapidly and returned to work; but rheumatism is comparatively a rare complication in gonorrhœa, and such cases as develop it are all cases who have been treated outside the clinic and to whom no vaccine has been given.

The conclusions which the writer has formed regarding the use of detoxicated vaccine in the treatment of gonorrhœa are :—

(1) That the patient rapidly improves even under adverse conditions and where the opportunities for giving irrigations are few.

(2) That the patient does not develop posterior urethritis to nearly the same extent, and the general results of the battle between the organism and the tissue are much less marked than when it is not used, and there is not the same amount of folliculitis, or the same tendency to soft strictures.

(3) That the likelihood of setting up a chemical urethritis is done away with, for it is not necessary to use strong solutions; and indeed there is no justification for their use, for even supposing a strong irrigation be given there is no reason to believe that the mucous membrane of the urethra will absorb any of the irrigating fluid, and so allow it to act on the deep-seated gonococci.

(4) That the only sound method of dealing with the deep-seated gonococci is by raising the bodily resistance, and this can only be done satisfactorily by giving large doses of vaccine, and that vaccine must be detoxicated.

(5) That rheumatism does not develop in cases where vaccine is used, and in cases where it has developed owing to the patient not having been treated, it is easily curable.

(6) That the patient can be given such dosage as will rapidly raise his resistance without ill effects. A child of ten can be given 2500 millions to start with.

Intravenous Administration of Detoxicated Vaccine.—Following the satisfactory results obtained by the usual method of subcutaneous injection of vaccine, the writer recently carried out the injections intravenously in the hope that the beneficial effects would evidence themselves more rapidly. Twenty cases were taken as they appeared for treatment at the clinic, so that the effect of the vaccine on both acute and chronic cases could be seen.

The technique employed was that of Besredka, in which a small desensitising dose of 250 detoxicated organisms was injected intravenously and the patients were allowed to rest for thirty minutes, when the larger doses were given. The idea was to obtain the maximum dose that could be given intravenously without causing violent reactions, and at the same time to note the effect of the vaccine on the disease.

The first case treated was one of chronic gonorrhœa in a patient who had contracted the disease three years previously and who had had intermittent treatment both by private practitioners and at venereal disease clinics during this period. Incidentally he had a hypospadias, a condition in which the writer has found that a rapid cure is very difficult to obtain. This patient attended the clinic in August 1920 and complained of rheumatism and a discharge, the examination of which showed gonococci. He was treated with detoxicated mixed organisms vaccines and his rheumatism improved, but he still showed gonococci in his discharge, and had recurrent attacks of rheumatism, which were relieved by vaccine. In March 1922 he was given 250 organisms intravenously as a desensitising dose, and thirty minutes later 20 million organisms were given. He had no reaction, but said his rheumatism was better.

Seven days later 100 million organisms were given with no desensitising dose; no

reaction followed. Four days after the second injection he was given a dose of 15,000 millions, as by this time it had been found that the other patients had felt no ill effects after being given a desensitising dose, and thirty minutes later 10,000 million organisms. The large dose of 15,000 millions caused the patient to complain of feeling feverish.

Four days later 15,000 millions were again given with no reaction, and three days after this the dose was increased to 20,000 millions. Another four days elapsed, when 25,000 millions were given, and four days later the dose of 30,000 millions. No reaction followed any of these injections, although all were given intravenously. About 12th April 1922 the patient transferred to another clinic, but only attended once during five months, after which he again reported to the writer's clinic to say that he has had no rheumatism and no discharge. He has since had all the tests made, and as no evidence of gonorrhoea can be found he has been discharged as cured.

The other 19 cases were injected in a similar manner, but the desensitising dose was increased to 300 organisms, and the large secondary dose was increased in every case as the results of reaction were seen. It was found that a dose of 10,000 millions could be given with safety, but that a dose of 15,000 millions produced rather marked reactions when given thirty minutes after the desensitising dose. In no case did the reactions vary much: a rigor starting about three hours after injection, followed by severe headache; pains in the joints of both arms and legs, and a feeling of sickness, which in one case was followed by vomiting. Two cases had to stop work for three days. It was found that when the initial large dose was not more than 10,000 million organisms the reactions were nil, and the dosage could be increased every five days by 5000 or 10,000 millions with no reactions.

One case was given an initial dose of 10,000 millions following the small desensitising dose, and this was increased by 10,000 millions every seven days till a dose of 80,000 millions was given, at which point the patient complained of feeling feverish and slightly off colour for about three hours after the injection.

As in all clinics the difficulty is to get the patients to attend till a cure is completed, so in this series of cases the results cannot be stated, as many of the patients absented themselves before the cure was completed.

The results were at first rather startling, for in most cases the discharge decreased markedly, and in one or two cases it stopped within a few days, and through this the patients believed they were cured and absented themselves.

Two cases carried out the treatment till a cure was obtained and were discharged, but in no case was a record cure in point of time obtained. It is admitted that certain cases tend to clear up early, probably on account of their own bodily resistance being strong; and for this reason, and because many of the patients absented themselves, the writer can give no definite statement as to rapidity of cure by this method.

The definite result obtained is that with a small desensitising dose of 300 detoxicated organisms a dose of 10,000 million detoxicated organisms can be given intravenously with perfect safety and with no reactions thirty minutes later, and this dose can be increased every five or seven days by 10,000 millions until a maximum of 80,000 millions has been reached; and if owing to the incompleteness of the records little has been proved as to the curative effects of the intravenous method, much has been proved as to the non-toxicity of the detoxicated vaccine.

CHAPTER XXXIII

SERUM THERAPY (PASSIVE IMMUNISATION) IN GONORRHŒA

BRUCKNER, Christéanu and Cinca (1906) produced, by injecting various strains of gonococci into a horse, an anti-gonococcus serum which proved to be a preventive and curative agent in the case of experimental gonococcal septicæmia in animals.

Rogers (1906) produced an anti-gonococcal serum by injecting the gonococcus into animals. These were inoculated once weekly for ten weeks. By injecting this anti-serum into gonococcal subjects, Torrey (1906) claimed that he was able to cure cases of acute gonorrhœal arthritis, epididymitis and prostatitis. It had little effect, however, in uncomplicated cases of urethritis. He administered the serum subcutaneously in doses of 2 to 6 c.c. at intervals of forty-eight hours to seven days.

Gibney (1906) reported on curative results with this anti-serum.

Soltan, Fenwick and Parkinson (1906) treated cases of gonorrhœal rheumatism and gonococcal pyæmia with anti-streptococcus serum given per rectum, and maintained that the disease in every case was cured within a few days. Campbell Williams thought that this supported the idea that a gonorrhœa was a mixed infection.

Fox (1906) also claimed good results from anti-streptococcus serum in some cases of gonococcal arthritis.

Rogers and Torrey (1907) recommended the use of a polyvalent anti-gonococcus serum prepared by injecting many strains into animals. At first rabbits were employed, but later they used rams, as it was found that injections of the rabbit serum produced alarming symptoms. The anti-serum did not appear to benefit cases of urethritis, vaginitis or conjunctivitis, because, perhaps, the circulating blood was unable to reach the germs in these mucous membrane affections. They considered, however, that good results should be obtained in all complications such as prostatitis, epididymitis, salpingitis, arthritis, iritis, pleurisy, endocarditis and meningitis. It is recommended that 2 c.c. be injected subcutaneously into the upper arm every other day. They give the following results with cases treated in this manner :—

Arthritis : 11 cases cured with three to four injections.

Teno-synovitis : 6 cases—4 cured.

Epididymitis : 8 cases—6 cured in a few days, 1 much improved and 1 not affected.

Cystitis : 1 case—cleared up in six weeks.

Chronic urethritis : did not yield readily except in 1 case.

Conjunctivitis : not benefited by injection or local applications of the anti-serum.

Iritis : promising results in 2 cases.

They state that the first injection of the anti-serum may cause a transitory increase of the discharge, or increase of pain and swelling in affected joints. These symptoms, they consider, may be due to the disintegration of large numbers of gonococci with consequent liberation of endo-toxin. They found no evidence that the serum was in any sense an anti-toxin.

Rogers (1907) recommended 2 c.c. of the serum as an injection every two to six days.

He stated that the results were good in early cases of arthritis, but that it had no effect in chronic cases or in cases of urethritis.

Torrey (1907) used the serum in 70 cases of gonococcal arthritis. Of these 78 per cent were entirely cured or much improved. Twenty were cured in ten days or less, after an average of five injections. This observer was able to demonstrate the presence of agglutinins and precipitins in the anti-serum used.

Porter (1907) treated 6 cases of severe gonococcal rheumatism with anti-gonococcus serum, and claimed rapid cures.

He injected 25 c.c. about every two to three days. Some were cured after three injections, others required six. The injections produced, as a rule, a local reaction and a temperature of about 101.2°F . In all cases gonococci were found in the urethral discharge; the latter condition as a rule diminished after the injections, and cleared up more quickly than usual.

Herbst (1908) treated 52 gonorrhœal cases with anti-serum with the following results:—

Acute urethritis, anterior and posterior: 17 cases—no results.

Subacute urethritis: 9 cases—no improvement in 8; 1 cleared up after the third injection.

Chronic urethritis: 11 cases—no improvement in 7; 1 cleared up in four weeks after eight injections, 1 in three weeks after six injections, 1 in two weeks after two injections.

Acute epididymitis: 4 cases—no improvement in 3; 1 cleared up in two weeks after six injections of 4 c.c. each.

Acute arthritis: 4 cases—little change produced.

Chronic arthritis: 7 cases—all improved after the first few injections.

Herbst concludes that the anti-serum is of most value in chronic gonorrhœal arthritis, but that it has little effect in acute cases.

Swinburne (1908), using Rogers and Torrey's serum (Parke Davis & Co.), got good results in cases of epididymitis and arthritis.

Uhle and MacKinney (1908) treated 23 cases of gonorrhœa with the above anti-serum, and obtained good results in 3 cases of arthritis. The pain was promptly relieved, and all local evidence of inflammation had subsided in less than two weeks. In the remaining 20 non-arthritic cases, including epididymitis and prostatitis, however, no improvement occurred. The serum was administered intramuscularly in doses of 2 c.c. The injections were always painful, and a general urticaria was produced in 7 cases.

Gayler (1908) described a case of gonorrhœal arthritis in a woman, treated with Rogers and Torrey's anti-serum. Prompt and decided relief was obtained in the joints, and the condition was cured after three injections. It had no effect, however, on the vaginal discharge, and gonococci continued to persist in the cervical secretion.

Baumann, Myers and Belfield (1908) each agreed that the anti-serum was valuable in the treatment of gonorrhœal rheumatism.

Butler and Long (1908) had no success whatsoever with the anti-serum treatment, and were against it.

Fletcher (1909) considered that it was valueless.

Bruck (1909) used a polyvalent anti-serum obtained from rams after they had been injected with many strains of gonococci. This anti-serum contained strong complement-deviating and agglutinating substances, but it had no destructive effect on the gonococci *in vitro*. He did not find that it was of any value as a therapeutic agent in the treatment of the disease. He also used the anti-serum of Rogers and Torrey (Parke Davis & Co.), but was unable to notice any good results even in cases of epididymitis and arthritis.

Perez-Miro, Swinburne, Rosenthal, Chassaignac, Parsche, Krist, Ebright and Plummer (1909) all believed that the anti-serum was of therapeutic value in cases of gonorrhœal arthritis.

Ballenger (1909) claimed to have obtained a curative result with the anti-serum in 72 per cent to 80 per cent of 90 cases of gonococcal arthritis. He considered further that it was efficacious in the treatment of prostatitis and cystitis.

Thomas (1910) agreed with Uhle and MacKinney in that he was unable to note any beneficial results with anti-gonococcus serum in the treatment of acute gonococcal infections, also no benefit in either the acute or chronic stages in the genito-urinary tract. He considered, however, that good results were obtained in chronic gonococcal arthritis.

Louis, Stellwagon, Herbst, MacKinney, Leschnew and Schmidt (1910) each agree that anti-gonococcus serum is valuable in gonorrhœal rheumatism.

Zigler (1910), on the other hand, was unable to note any good results in gonorrhœa with injections of the anti-serum.

Masson (1910) reported on the effect of anti-serum in one case of acute gonorrhœa in the female. He considered that it produced a complete cure in seventeen days. Five days after the first injection the vaginal discharge had ceased and no gonococci could be discovered. In fourteen days the local symptoms had completely subsided.

Lydston (1910) reported a successful cure in a child. It developed gonorrhœal conjunctivitis forty-eight hours after birth. On the fourteenth day the left wrist was attacked, and on the seventeenth day the right knee. He administered anti-gonococcal serum in doses of three minims every other day, gradually increasing to fifteen minims. The reaction was slight and the improvement was prompt. In four weeks the joints were almost normal. The only other treatment used was anodyne ointment applied locally.

East-Orange (1910) recorded a case of acute gonorrhœal salpingitis which was rapidly cured by 6 c.c. of anti-gonococcus serum. Warm iodine vaginal douches were also given. The patient was discharged cured in seventeen days.

Orton (1910) reported on one case of acute gonorrhœal salpingitis, in which the fever at once disappeared after an injection of 2 c.c. of anti-gonococcal serum.

Salter (1910) described a case of chronic gonorrhœa which responded remarkably to anti-streptococcus serum given per rectum after failure with all other usual remedies. Six months after the initial infection a course of vaccine treatment was given. This cleared up the prostatic symptoms, but the discharge was apparently uninfluenced and remained profuse. He then injected 10 c.c. of polyvalent anti-streptococcus serum per rectum, and repeated the dose on two successive days. This was followed by immediate and marked improvement. The discharge ceased entirely for two weeks, but, as a slight purulent discharge then reappeared, he repeated the rectal injections three times. After this the purulent discharge cleared up, a little mucous discharge only remaining in the morning.

McNeil wrote an article on the serotherapy of gonorrhœa. Unfortunately the writer has not been able to gain access to his work.

Fisichella (1911) used a serum prepared from a horse at the Serotherapy Institute, Milan. He was unable to get any results in cases of urethritis, but it seemed to be good in arthritis cases.

Ramond (1911) employed auto-serotherapy successfully in 5 severe cases of gonococcal arthritis. He injected several times from 1 to 5 c.c. of fluid obtained by puncturing the joint. The injections were made subcutaneously near the joint in question. Maillet reported similar experiences, and also Constantinescu in connection with hydrarthrosis.

Abdulow (1912) tried serum-therapy in 7 cases, and concluded that anti-gonococcus serum had no marked influence either in acute or chronic gonorrhœa. The best therapeutic results were obtained in chronic arthritis. The favourable effect of the serum showed itself in the rapid disappearance of joint pains, and it caused the course of the disease to be milder in character. In nearly all cases the serum injections produced a local and general urticaria, but rises of temperature occurred only exceptionally. There was no albuminuria observed, nor any disturbance of the heart's action as a result of the treatment.

Héresco and Cealic (1912) obtained good results in the treatment of gonorrhœal rheumatism by injecting anti-meningococcus serum.

Lasserre (1913) also used anti-meningococcus serum, and claimed to have got good results in subacute gonococcal arthritis with a tendency to septicæmia. Cases of acute arthritis with effusion or a tendency to ankylosis, as well as chronic forms, were often favourably influenced by it. He recommended four or five injections into the buttocks every four or five days.

Masson (1913) reported a case of salpingitis cured by the injection of anti-meningococcal serum.

Herescu and Strominger (1913 and 1914), on the grounds that the meningococcus closely resembled the gonococcus morphologically, investigated the effect of anti-meningococcus serum on gonorrhœal complications. They found that it produced most excellent therapeutic results in cases of gonococcal arthritis, ophthalmia, septicæmia, uretero-pyelitis, and meningitis of gonorrhœal origin.

Schmutz (1913) reviewed the various measures in vogue for treating the complications of gonorrhœa, particularly epididymitis, and related extensive experience in his own and others' practice with anti-meningococcus serum, particularly in France and Roumania. The serum was generally injected into the muscles of the thigh, and three injections were usually sufficient. The spontaneous pain was the first symptom to subside under this serotherapy; the patients slept well after the first night, and the epididymides became less sensitive. The temperature as a rule fell the day after the injection, and at the same time the inflammation became less angry. The swelling of the deeper tissues began to subside in two or three days. The effusion in the tunica vaginalis noticed in 9 out of 50 cases was all absorbed, and in some instances this occurred within forty-eight hours after the injection of the serum. By the tenth day the epididymis was soft throughout. In 5 out of 6 patients examined later, the epididymis was apparently normal in every respect, but the sixth had still a tiny hard lump, probably retreating at the time. He concludes his review by recommending anti-meningococcus serum as a very excellent remedy for gonorrhœal epididymitis. In his opinion the only contra-indications are possible anaphylaxis due to previous serotherapy, and cases with mixed infection in which good results cannot be expected.

Waeber (1913) treated 6 cases of gonorrhœa in women with anti-gonococcal serum prepared in the Bern Institute. He was unable to observe any benefit as a result of the injections.

Debré and Paraf (1913) are in favour of serum therapy in gonorrhœa, and consider that a great future lies before it. They obtained a very active anti-serum from rabbits which were immunised with increasing doses of gonococci given alternately subcutaneously and intravenously. They measured the potency of this anti-serum by its power of protecting a rabbit against injections of 200 to 300 millions gonococci into the anterior chamber of the eye. These inoculations always produced a panophthalmia. When, however, their anti-serum was injected into the eye simultaneously with or several hours after the injection of gonococci, no harm resulted, showing that the anti-serum was able to protect the animals against the infection. These researches were confirmed by similar experiments on monkeys. They think that the anti-serum should be injected in different places according to the site of the disease; thus they obtained excellent results with intra-urethral injections in 2 cases of acute urethritis.

Demskaja (1913) saw no beneficial results in urethritis or vaginitis, but good results in joint complications.

Cholzoff and Graminitzky (1914) wrote a paper on the subject, but the author has been unable to gain access to it.

Chiari (1914), in his review on gonorrhœal arthritis, states that in the literature he found reports of 16 cases treated with anti-meningococcus serum, and of these 13 were cured.

Corbus (1914) states that prior to 1911 he was in the habit of giving doses of 6 to 12 c.c. every two days in cases of acute epididymitis, with splendid results. He got a complete cure in a case of prostatitis and arthritis in two weeks by injecting 16 c.c. in three days. After this he adopted the plan of giving large doses by the intravenous route as recommended by Cole (1913) in the case of anti-pneumococcus serum, and by Weaver (1913) in the case of anti-streptococcus serum. Corbus controlled his results in gonorrhœa by the complement-fixation test, and the following are the details of 24 cases treated with large intramuscular doses of anti-gonococcus serum (Parke Davis & Co.) :—

Acute anterior urethritis : 5 cases—no improvement.

Chronic anterior and posterior urethritis : 5 cases—rapid improvement.

Prostatic abscess : 1 case—rapid improvement.

Arthritis and epididymitis : 1 case—marked improvement.

Acute arthritis : 4 cases—rapid improvement, but 1 relapsed.

Chronic arthritis : 4 cases—1 marked improvement (36 c.c. given), 3 slow improvement (18 c.c. given).

Chronic endometritis : 3 cases—rapid improvement and apparent cure.

Chronic endometritis and salpingitis : 1 case—rapid improvement and apparent cure.

He drew the following conclusions from his investigation :—

(1) The complement-fixation test is a reliable guide in the administration of the serum. When the test is negative the serum should not be used.

(2) The intensity of the complement-fixation reaction is a reliable guide as to whether or not the serum will be efficient. The more strongly positive the reaction the more efficient is the serum likely to be.

(3) The amount of the anti-serum injected should be at least from 36 to 45 c.c. administered intramuscularly, usually 12-15 c.c. each day for three days.

(4) Serum sickness, if distressing, should not be alarming.

(5) A negative complement-fixation test after two to three months shows a complete cure.

All his injections were intramuscular except one.

Bowers (1915) states that while the gonococcus is the primary cause of many pelvic infections in women, yet it is sometimes complicated with the streptococcus. In such cases he recommends that 50 c.c. of anti-streptococcus serum should be given every six hours until a favourable reaction occurs.

Ganjoux (1915) used anti-gonococcus serum in gynæcological and obstetrical cases with some good results.

Boyd (1915) reported on 2 cases of gonorrhœal uretero-pyelitis treated with injections of anti-meningococcus serum. The writer, however, has been unable to get access to his paper.

Malleterre (1916) also used anti-meningococcus serum in gonorrhœal rheumatism with some success.

Cano, Townsend and Valentine (1917) described a method of treating gonorrhœa by intravenous and intraprostatic injections of methyl phenol and normal phenol serum.

Paraf (1919) obtained good results in localised gonococcal infections—arthritis, orchitis, etc.—with anti-gonococcal serum.

Debré and Paraf (1919) injected anti-gonococcal serum into the joints of 15 patients with different forms of recent gonococcal rheumatism. In 6 cases the cure was complete in less than eight days. Eight other cases were cured before the fifteenth day. In one case no benefit was derived. This patient was a pregnant woman in bad health. They punctured the joint and injected the anti-serum in place of the evacuated effusion and then applied a compression dressing. The injection was repeated every day, or every second or third day. In six of the cases several joints were affected, and all of these joints were injected

with the anti-serum at the same time. They state that this local serotherapy has to be supplemented with intramuscular or intravenous injections of the anti-serum in order to produce a general immunity and to prevent the involvement of other joints. The local serotherapy is limited to the larger joints, as it is practically impossible to inject the anti-serum into a small articulation. They say that they have never had any reason to believe that there are special strains of gonococci.

Widal and May (1920) reported the recovery under anti-gonococcus serum of a woman of 30 suffering from gonococcus septicæmia and jaundice.

Reenstierna (1920) prepared an anti-gonococcus serum from rams. To this serum he added some agent for causing a febrile reaction (usually killed typhoid bacilli). This material, when injected directly into the site of gonorrhœal abscesses, usually caused a quick cessation of pain and ultimate cure. He also used this combined serum-vaccine treatment in 100 cases of different complications, especially arthritis, epididymitis and prostatitis. The results were extremely satisfactory in the majority of cases. In a very few cases no benefit was apparent, and he thinks that a secondary infection was probably responsible for this. Prostatitis was generally cured in a week. Good results were also obtained in gonococcal disease of the eyes, adnexa, infiltrations of Bartholin's glands and peri-urethral infiltrations. Painful symptoms decreased or completely disappeared five or six hours after the injection.

Ivens (1921) treated women with subcutaneous and intraperitoneal injections of anti-gonococcal serum. In some cases with cervicitis and profuse leucorrhœa he used serum packs in the vagina. The results were very good, but two cases relapsed after some months of good health. One acute case did not derive any benefit from the treatment.

Ramond (1921) refers to the pseudo-phlegmonous form of gonorrhœal arthritis and extols the fine results he has obtained by anti-gonococcus vaccine and anti-meningococcus serum, either alone or associated. He states that this treatment may save a joint from an otherwise inevitable ankylosis.

Schachmann (1922) reports very favourable results from subcutaneous injections of the patient's own blood serum in 15 cases of acute gonorrhœa and in 5 cases of gonococcus ophthalmia neonatorum. The ophthalmia subsided remarkably promptly. The dose of serum injected was 1.5 c.c.

Schmidt and Walther (1922) have employed rather an extraordinary method of treatment, as follows:—(1) Five c.c. of boiled milk is injected either subcutaneously or intramuscularly. This produces a febrile reaction which is at its height about six to eight hours after the injection. (2) A serous exudation is artificially induced at the site of the disease by means of a drug called ethyl-morphine hydrochloride. (3) This serous exudate is collected and re-injected into the patient.

Schmidt is an ophthalmologist, and states that this mode of treatment is amazingly effective in gonococcal eye affections. He calls this triple method the "*heilfieberserum-stauung*." Walther describes its application in 53 cases of gonococcal urethritis with a cure in 41 per cent of the cases. To induce the serous exudate during the height of the febrile reaction, he injects 10 c.c. of a 10 per cent solution of ethyl-morphine hydrochloride, and this solution is held in the urethra for ten minutes.

In Walther's 53 cases no benefit was apparent in very early acute gonorrhœa of less than one week's duration. In cases, however, of eight weeks' standing and over, beneficial results were obtained in 100 per cent of the patients.

Author's Conclusions regarding the Serum Therapy of Gonorrhœa.—In reviewing the above literature on the subject, it will be ascertained that 43 out of 50 observers considered that anti-gonococcus serum was of some value, while only 5, or 10 per cent, believed that it was of no value whatsoever. The great majority of the articles on the subject maintain that the anti-serum is of no value in cases of uncomplicated gonorrhœa, and that its use is limited to chronic gonococcal joint affections. A certain number, however, obtained good results also in such complications as epididymitis and salpingitis, and even

in prostatitis and cystitis. The consensus of opinion on the whole, however, suggests that it has no curative effect in gonorrhœa of the mucous membrane.

With regard to the anti-streptococcus serum, four observers have reported good results. It is difficult to understand how this non-specific anti-serum should be of value, unless it is supposed that the cases in question were complicated with a streptococcus infection. On the other hand, the curative effect might be attributed to protein shock or anaphylaxis. Certain authors of recent years have maintained that this so-called "protein shock" stimulates the system to throw off a disease (see Smith (1916), chapter on Vaccine Therapy).

Eight authors have recorded good results arising from the administration of anti-meningococcus serum in gonorrhœal conditions. It is quite probable that this anti-serum might be of some value, because the meningococcus is very closely allied indeed to the gonococcus. The complement-fixation test brings out this close relationship very clearly. The serum of a person suffering from cerebro-spinal meningitis gives a positive complement-fixation reaction with a gonococcus antigen, and *vice versa* a meningococcus antigen very often gives a positive reaction with the serum of a gonorrhœal subject. It is quite possible, therefore, that an anti-serum against the meningococcus might have a certain influence against the gonococcus as well.

In recent times there has been a prevalent belief that anti-gonococcus serum is valueless. This opinion, however, is hardly fair considering the literature on the subject. It ought to be conceded that it has some use at least in the treatment of joint complications. All seem agreed that anti-meningococcus serum is valuable in the treatment of cerebro-spinal meningitis, and in view of the close relationship of the meningococcus to the gonococcus it would seem reasonable to believe that an anti-gonococcus serum should be of some value also in gonorrhœa. The evidence, however, is not sufficiently good to warrant its use in all cases. It should be reserved for those complicated cases which have failed to respond to other measures such as vaccines, etc. It is a bad policy to inject anti-serums of doubtful value, because of the danger of anaphylaxis at a future date when it may be necessary to inject a useful anti-serum, as in the event of diphtheria, etc. The previous injection of useless serum may be the cause of anaphylactic shock, which might jeopardise the patient's life when a well-recognised anti-serum is indicated and injected. Apart from this, anti-sera as a rule cause a considerable amount of pain and discomfort, and often produce urticarial rashes. For this reason alone it is bad policy to inject them when they are of doubtful value. In short, anti-gonococcal serum is contra-indicated except in those complicated cases of gonorrhœa which have resisted all other treatment.

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CHAPTER XXXIV

CHEMICAL TREATMENT OF GONORRHŒA

ANTISEPTICS—SILVER SALTS—BILE SALTS—ACRIFLAVINE—AUTHOR'S EXPERIMENTS—
CHEMICALS ACTING THROUGH THE BLOOD STREAM—COLLOIDAL PREPARATIONS

NUMEROUS chemicals, more especially antiseptics, have been tried and recommended in the treatment of gonorrhœa. The majority of these are used locally in the form of irrigations or instillations. In many cases the gonococcicidal action of these chemicals has been tested by experiments outside the body.

Steinschneider and Schäffer (1894) endeavoured to ascertain the bactericidal power of several antiseptics against the gonococcus, by acting upon the live germs with a certain dilution of each agent for a given time. A small quantity of the material was then inoculated on to a suitable culture medium and incubated. If no colonies appeared, it was assumed that the gonococcus had been killed. They gave the following table showing the results of their experiments :—

Antiseptics.	Concentration.	Result on Culture Medium after	
		Five Minutes' Contact.	Ten Minutes' Contact.
Silver nitrate	1 in 1,000	0	0
	1 „ 4,000	A few colonies	0
Argentamin	1 „ 2,000	0	0
	1 „ 4,000	0	0
Argonin	1 „ 4,000	0	0
Protargol	1·5 per cent	A few colonies	0
	1 „	„ „	0
	0·25 „	Considerable numbers of colonies	One colony
Mercuric chloride diluted 1 in 10 with saline	1 in 10,000	Some colonies	One or two colonies
	1 „ 20,000	A few colonies	Four to five colonies
Oxycyanide of mercury	1 „ 3,000	0	0
Potass. permanganate	1 „ 1,000	Numerous colonies	Numerous colonies
	1 „ 2,000	„ „	„ „
Zinc sulphate	1 „ 400	„ „	„ „
Ammonium ichthyol sulphonate	1 per cent	Several colonies	One colony
	2 „	Four to five colonies	0
Resorcin	2 „	Moderate number of colonies	A few colonies
	4 „	A few colonies	0

They concluded that the silver salts were relatively potent, more especially as they could be used in high concentration. The silver preparations have been used most extensively in the local treatment of gonorrhœa, and silver nitrate would appear to be

one of the best. One of the advantages claimed for the silver salts is that they remain behind in the urethra and exert their influence for many hours after the injection. After a prolonged injection one can certainly detect the silver compounds in the urethral secretion from twelve to fifteen hours later (Koch, 1912).

Finger, Ghon and Schlagenhauser (1894) experimented on the bactericidal effects of various antiseptics, by allowing them to come into contact with serum-agar cultures of gonococci for two minutes. It was found that potassium permanganate (1 in 1000), carbolic acid (1 in 1000), mercury perchloride in saline (1 in 5000), and silver nitrate (1 in 1000), all failed to destroy the cultures. They believed that the above solutions were unable to penetrate into the deeper layers of the culture because the chemicals in question coagulated the albumin and thereby prevented further penetration. Chemical investigations carried out on the gonococcus in artificial culture outside the body are somewhat erroneous and misleading. In such circumstances the antiseptic gets at the germs readily, whereas in the urethra the chemical may never reach them, because they are enveloped in pus, and also because they are often deeply situated in the glands and in the submucous tissues.

Careful researches, however, have been carried out with regard to the penetrative power of chemicals into the tissues themselves, and in this way one is better able to judge their value in local treatment.

It is well known that the tissue fluids contain albumin and sodium chloride, both of which produce insoluble compounds with many antiseptics such as perchloride of mercury and silver nitrate. These chemicals therefore are not only neutralised by the tissues, but the insoluble compounds formed act as a barrier against their penetration to the deeper layers. In consequence the gonococci which are lying deep down between the epithelial cells of the mucous membrane and those in the superficial submucous connective tissues may never be reached.

Schäffer and Steinschneider tested the bactericidal potency of silver nitrate and perchloride of mercury on the gonococcus, by mixing these antiseptics with ascitic bouillon cultures of the germ (the ascitic bouillon was brought to the same consistence as the tissue fluids, so far as salt content and albumin was concerned). They found that under these conditions the chemicals were thrown out of solution and rendered more or less inactive by their combination with the albumin and sodium chloride. Hence the bactericidal potency in such circumstances was very much less than was the case when the gonococci were simply suspended in water.

The table given above shows the results obtained by these authors when using ascitic bouillon cultures. It will be noted that silver nitrate under such conditions was less potent than argentamin, argonin and protargol, more especially as the latter preparations can be used in much greater concentration than the nitrate itself in the actual treatment of gonorrhoea.

Another interesting and instructive series of experiments was carried out by treating uninoculated serum-agar for five to ten minutes with solutions of silver nitrate, perchloride of mercury, argentamin, carbolic acid, etc., in the concentrations mentioned above. The serum-agar was then washed with sterile water and inoculated with gonococci. It was found that the silver nitrate and mercury perchloride produced a more deleterious effect on the culture medium than the other chemicals, because they had entered into combination with the albumin and salts on the surface, thereby destroying its nutritive properties. From such experiments one would surmise that these antiseptics were injurious to the tissues.

In a further series of researches Schäffer (1896-97), Finger, Casper (1898) and Scholtz (1904) attempted to settle how far solutions of various antiseptics could penetrate into the tissues, as this was obviously an important point in the treatment of gonorrhoea.

Schäffer placed pieces of kidney and liver, freshly excised, in solutions of silver nitrate and argentamin for a given time, and then cut sections. The cut surfaces were

exposed to the light, causing the silver salts to become blackened, and in this way it was ascertained how far the chemical had penetrated. Under these conditions it was clearly shown that the argentamin had a far greater power of penetration than silver nitrate. The inferiority of the silver nitrate is due to its great capacity for forming insoluble compounds with salt and albumin, and hence it builds up a barrier against its own penetration. Dead tissue of course is different from live tissue, so that one cannot entirely trust these penetration experiments without making further investigations on the living mucous membrane itself.

Further researches, however, were made by Finger, Casper, Lohnstein and Wildbolz on the urethra and conjunctiva of living animals.

Casper and Finger attempted to establish the depth to which silver nitrate could penetrate in the urethral mucous membrane of dogs. A solution of 2 per cent was injected into the urethra, and it was shown by sections exposed to the light that the silver was able to reach the lowest layers of the epithelium, and even further into the superficial layers of the submucous connective tissue.

In acute gonorrhœa, however, it is necessary to use in practice a solution much weaker than 2 per cent (50 to 100 times weaker), so that no very definite therapeutic conclusions can be drawn from their experiments.

Finally, Scholtz made the following investigations on patients suffering from acute gonorrhœa at his clinic in Breslau. He injected protargol (1 per cent to 3 per cent), also silver nitrate and argentamin, etc., in the usual manner, and allowed the solution to remain in the urethra for twenty to thirty minutes. After this the injection was evacuated, and the urethra was washed out several times in order to remove the residue of the antiseptic. The superficial layer of the mucous membrane was then carefully scraped away with a platinum loop or a little spoon, and one half of the material so obtained was examined microscopically, whilst the other half was inoculated on to a good brand of culture medium. The microscopic examination showed more or less numerous gonococci, but the cultures remained practically sterile. Scholtz concluded from this that the gonococci which were present as proved by the microscopic examination were dead, and had been killed by the injection. He was justified in this deduction, because when ordinary pus containing gonococci was inoculated on to a good medium the germs very seldom failed to grow, even when by microscopic examination the gonococci appeared to be quite scanty in numbers. It can be concluded at all events from these experiments that the silver salts, when used in a strength suitable for urethral injection, are able to kill quickly and with certainty those gonococci which are lying on the surface of the mucous membrane. Clinical observations, however, showed that the disease was not yet cured, so that apparently the germs lying within the deeper epithelial layers had not been destroyed. Clinical observations have proved that these antiseptics, even when injected in the greatest concentration possible, are only able to kill off the superficial gonococci, and at the most only temporarily inhibit the multiplication of those more deeply situated.

Jadassohn maintains that the deeply-situated germs can only be destroyed by repeated and long-continued copious injections. This lack of penetrative power on the part of chemical antiseptics is abundantly proved by the attempts which have been made at abortive treatment. Successful abortion of the disease is only obtained when the injection is made within twenty-four hours after the earliest commencement of the symptoms, because at this early stage the gonococci have not yet had time to penetrate more deeply than the superficial epithelial layers.

The number of different antiseptics which have been recommended and used locally in the treatment of gonorrhœa is exceedingly great. Many of these have fallen out of use and been forgotten, only to be revived again at a later date. Furthermore, many different observers use different concentrations. Some believe in strong lotions, others do not. At present the consensus of opinion seems to be that local antiseptic treat-

ment is pushed too far, and that the error is on the side of over-treatment, whereby a chemical urethritis is set up by applications which are too frequent and too strong.

Many cases of chronic discharge which have been over-treated by local antiseptics for years will sometimes entirely clear up when such local treatment is entirely prohibited. For this reason local chemical treatment should always be controlled by the microscope. So long as gonococci are present in considerable numbers in the discharge it is wise to keep up fairly vigorous antiseptic irrigations or injections, but when the germs can no longer be detected the irrigations should be reduced from twice daily to once daily and then to twice weekly. The presence of much pus with no gonococci or other organisms is a good indication of chemical urethritis or over-treatment.

This subject will be discussed further at the conclusion of the author's experiments enumerated below.

Various forms of silver salts have for a long time been favoured in local treatment.

Rosenfeld (1913) recommended **hegonon** as a good and non-irritating antiseptic.

Bruck (1913) carried out experiments with a combination of silver with uranium, but was unable to find that such compounds were superior to the silver salts alone.

In the female one can use much stronger antiseptics than in the case of the male urethra.

Hingenberg (1913) used a **protargol** solution of 10 per cent for the urethra, vagina and uterus. He also recommended a solution of zinc sulphate and acetate of lead (one gramme of each in 100 c.c. distilled water) for the urethra. For the vagina he used the following lotion: Boric acid 3 grammes, camphor 3 grammes, alumenol 5 grammes, and glycerine 125 c.c. The treatment should be continued for three to six weeks.

The action of **bile salts** as an antiseptic towards the gonococcus is very interesting.

Lohlein (1909) noted that cases of gonorrhœal ophthalmia with icterus neonatorum cleared up very quickly. He also noted that bile salts (even 5 per cent solutions) were anti-gonococcal and acted as a solvent of the germ. Dufaux reported on a large number of observations with bile salts in treatment. He got excellent results with a silver compound of bile salts called "Choleval."

Hofmann (1912) carried out further researches on this matter. He used human bile as well as that from the ox, the pig and the dog. The pure salts were obtained by treating the bile with acetate of lead and ammonia. After filtration the precipitate was washed with water containing a few drops of ammonia. It was then dried over a water-bath, rubbed into a fine powder, made into a paste with alcohol, and heated over a water-bath till the alcohol boiled. The alcohol material was then filtered hot, and after the addition of sodium carbonate was evaporated to dryness in a porcelain dish. In this way the lead salt is changed into sodium glycocholate and lead carbonate. The lead and sodium carbonate are removed by extracting with rectified spirit. Finally, the whole was extracted with ether and allowed to stand. In a few days the so-called Plattner's bile-salt crystals separate out, consisting of glycocholate and taurocholate of soda. If the bile is treated with sugar of lead (subacetate) the precipitate contains glycocholic acid. If lead acetate is used one gets a precipitate of taurocholic acid. To separate the two is a complicated process. In order to simplify the procedure, Hofmann got rid of the cholesterin and bile pigment by extraction with hot alcohol and purification with animal charcoal. He then treated the remainder with sugar of lead. He used the bile salts so obtained in the treatment of acute gonorrhœa. Solutions of 1 to 2 per cent were injected into the urethra and held there for five to ten minutes. A slight but by no means striking reduction in the discharge was produced. When a 5 to 10 per cent solution was used he got a very definite result by about the second day. The discharge was considerably less and the number of gonococci definitely smaller. In isolated cases the gonococci disappeared completely, but returned again after suspension of treatment. He then tried the bile salts in combination with silver preparations, but was not successful in producing a bile compound with sufficient effect. He also tried other heavy metals, but the bile salt com-

pounds were insoluble and not effective. He finally tried injecting the bile salts, and followed this by an injection of silver salts. He considered that the gonorrhœa was definitely shortened by this method, more so than with the silver alone. He found that the bile salts were non-irritating. He stated that Dufaux's "Choleval" was good but too costly to use.

Maheu (1917) made microscopic observations on the urethral discharge of 34 men with gonorrhœa who had been given a course of treatment with intramuscular injections of **potassium permanganate**. Within a week the number of gonococci in each leucocyte had decreased, but the pus persisted as abundantly as before.

An important addition to the long list of antiseptics used in gonorrhœa are the flavine compounds discovered by Prof. Carl Browning (1917). These comprise homoflavine, proflavine, and **acriflavine**. They resemble picric acid in some respects, and are claimed to be highly antiseptic, non-irritating, and very penetrating. Watson claims that acriflavine is superior to potassium permanganate and the other antiseptics previously used, and believes that it shortens the duration of the disease very considerably when properly administered.

Davis and Harrell (1918) (Johns Hopkins Hospital) were strongly in favour of acriflavine, and maintained that from the scientific point of view it had the four following points of superiority over other chemicals :—

(1) Acriflavine is highly diffusible in the tissues ; it will penetrate through the mucosa of the urethra and the bladder.

(2) It is antiseptic in urine in higher dilutions than any other diffusible dye studied.

(3) It inhibits the development of gonococci in cultures in a dilution of at least 1 in 300,000, showing at least six hundred times the potency of protargol.

(4) It has a peculiar affinity for leucocytes, as shown by Fleming. Used clinically they state that urethral injections of concentrated acriflavine cause slight smarting, which persists for one hour or more, but patients previously treated with protargol say that acriflavine is decidedly less irritating.

The most satisfactory concentration is 1 in 1000, and with this strength the smarting is almost negligible, and it is just as efficient as the more concentrated solutions.

In *anterior cases* they injected 3 c.c. of a 1 in 1000 solution into the anterior urethra and allowed it to act for five minutes.

In *posterior cases* 15 to 30 c.c. are injected through into the bladder, distending the urethra, and retained in the urethra for five minutes and in the bladder until the next voiding of the urine.

They recommend that the injections be given twice a day until all organisms have disappeared from the discharge, and then once a day until the patient is considered well. Their results were all controlled by daily microscopic examinations, and by the three-glass test.

The results obtained by their treatment were as follows :—

(1) The organisms frequently disappeared from the discharge following a single injection, and did not return during the subsequent course of the disease. In the majority of cases they had disappeared after two or three injections. In a few cases reappearance of the germs has occurred, but continued treatment soon caused disappearance.

(2) The discharge is markedly decreased from the beginning, and very quickly becomes thin and mucoid. It has usually disappeared by the fifth day.

(3) In cases of anterior and posterior urethritis the posterior infection usually improves before the anterior. Trigonal inflammation quickly subsides. Frequency of micturition is often entirely relieved by a single injection, and nearly always by two to three.

(4) Some of the dye evidently remains in the urethra for a considerable time. The discharge at the end of twenty-four hours is still stained a brilliant yellow, and microscopically many of the leucocytes are well stained. The urine is definitely yellow, and is fluorescent even at the end of thirty-six hours.

(5) "A striking feature of this form of therapy is that in many cases the dye acts almost as a specific, while in an occasional one it seems without any effect whatever." The cause of this is not determined.

The authors conclude that "the average duration of a gonorrhoea under this treatment is distinctly less than with the usual methods."

Certain other observers are not so favourably disposed to acriflavine. Col. Harrison, in a series of cases at the Military Hospital, Rochester Row, did not find that it showed any superiority over potassium permanganate.

Lees (1919) was of the same opinion, and states that he has seen many intractable chronic gleet in cases which had been treated with acriflavine. The author gave acriflavine a careful trial in a very resistant chronic case, but was able to find gonococci in the discharge, after prostatic massage, in spite of persistence in treatment. One disadvantage of acriflavine is that it colours everything yellow, such as the linen, fingers, etc.

Armstrong (1919) disagrees with the observations of Davis and Harrell with regard to acriflavine. He used this antiseptic in 23 cases of uncomplicated gonorrhoea, carrying out the exact regime laid down by them. Of these 23 cases, 6, or 26 per cent, showed that at the end of three weeks Gram-negative diplococci, morphologically indistinguishable from gonococci, and purulent beads, were present within twenty-four hours after stopping the injection. Of the remaining 17, 13, or 76 per cent, showed pus cells in their smears, and their anterior washes, when centrifugalised, had a purulent deposit. The remaining 4 showed mucus and epithelium. Far from causing only slight smarting at the strength recorded, the patients treated complained at the end of ten days of severe smarting and dysuria, which has never been a symptom in any cases treated with ordinary solutions of protargol. He found that in cases of submucous infiltrations or in soft strictures associated with gonorrhoea the remedy is apt to produce retention of urine. The fact of the urine remaining yellow for hours and the leucocytes being well stained is of little clinical significance.

Mann (1921) employs the technique of Watson, who uses acriflavine in a strength of 1 in 4000 in physiological saline at body temperature. The irrigation is given once daily. Mann regards this as being the best remedy for the irrigation treatment of gonorrhoea. In 36 cases carefully controlled it gave very good results in his hands. The author considers that in view of the very extraordinary gonococcicidal potency of acriflavine (see below) it should be given further trials clinically at a strength of about 1 in 3000, *i.e.* a dilution which does not coagulate albumin.

Maggiore (1919) reported on seven cases of infantile gonococcal vulvo-vaginitis in order to illustrate the advantage of treatment with **tannic acid** in powder form. The secretions in the vulva and at the opening of the vagina are washed off with potassium permanganate 1 in 20,000, and the parts dried with cotton-wool. A thick layer of tannic acid is then dusted over the privates and kept there by means of a pad and bandage. With this treatment he claims a cure in from one to three weeks.

Turner (1919) got good results with **picric acid** douches in the treatment of gonorrhoea in women.

Mobitz, W. (1920), had good results in the treatment of gonorrhoeal arthritis with **vuzin**. He states that joint puncture with lavage and injection of 1 in 5000 vuzin solution in gonorrhoeal rheumatism of the large joints has resulted in recession and cure of the infection. Only ten cases have so far been treated in this manner, but they all responded rapidly.

Stern and Ridler (1920) treated ten cases of gonococcal arthritis with intravenous injections of 20 c.c. of a solution of **sodium iodide** (2 grammes in 20 c.c. of water). The injection is repeated every four days. The result in all of the ten patients was remarkably good. Similar treatment was administered to cases of acute orchitis, with rapid disappearance of the acute symptoms. Good results were also obtained in prostatic infections.

They have records of 100 cases discharged as cured after this treatment, but they were unable to follow the subsequent history of these patients.

Foss (1920) reports on the treatment of gonorrhœa in women by local applications of a solution of **methylene blue** 1 gramme, glycerine 25 c.c., and water to 100 c.c. He believes that the methylene blue is a good antiseptic because of its great affinity for the gonococcus, and also because it is absorbed by the mucous membrane and even by the squamous epithelium. In acute and chronic cases the cervix is swabbed with a saturated solution of sodium bicarbonate in order to remove the mucus and discharge. A gauze plug 12 inches square is dipped for half its length in the solution, and this end is packed tightly against the cervix; the dry end rests loosely in the vagina. The plug is removed after twenty-four hours. This treatment is carried out for five days, and then for two days dry plugs are used. This rotation is continued as long as the discharge persists. There are two contra-indications for the use of this method, viz. pregnancy and the puerperal state. General treatment is carried out on the usual lines, and urinary antiseptics and gonococcal vaccine are administered.

The author is somewhat sceptical as to the efficiency of methylene blue as a gonococcicide, since he has found that the gonococcus is capable of growing on a culture medium faintly tinted with crystal violet (see Chapter XV.).

Davis and Swartz (1920) describe a new and practical method of testing the germicidal potency of various antiseptics against the gonococcus. They found that **sodium oleate** had a definite germicidal action on the gonococcus, and that where uncoagulated protein is present this action is increased by the addition of 0.5 per cent boric acid. The presence of small sublethal quantities of sodium oleate (1 in 8000) increases the germicidal action of many drugs against the gonococcus; with others it is without effect. Sodium oleate with boric acid is suggested as an adjuvant to other drugs in the treatment and prophylaxis of gonorrhœa.

Swartz (1920) states that the germicidal value of certain concentrations of a number of **local anæsthetics** against the gonococcus was determined by Macht and others. He himself tested them in solutions of the same strength as those commonly used in clinical work. Solutions of **beta-eucaine** were found to have no antiseptic or germicidal action against the gonococcus. **Alpha-eucaine** solutions are antiseptic but not germicidal for the gonococcus. **Holocain**, **alypin**, **apothésin** and **benzyl alcohol** are both antiseptic and germicidal for the gonococcus.

Young, White and Swartz (1919) tested a new germicide, called **mercurochrome-220**, against *Staphylococcus aureus* and *B. coli*, and laboratory tests proved it to be very efficient.

Swartz and Davis (1921) made tests with this chemical against the gonococcus and found it killed the germ in twenty minutes at a dilution of 1 in 16,000. It can be used in the urethra at a strength of 1 in 50 (2 per cent). Its germicidal value diminishes on standing for some time, and therefore for clinical use it should be freshly prepared. They found that the gonococcus was forty times more susceptible to the action of mercurochrome-220 than *B. coli*.

Swartz and Davis (1921) in a further series of experiments found that **silvol**, **cargentos**, **argyrol** and **protargol** have a definite but not a very potent germicidal value against the gonococcus. The **phenols**, **tricesols**, **potassium permanganate**, **zinc sulphate** and **boric acid** have in their opinion too little germicidal value against the gonococcus to be useful as germicidal agents in the urethra. **Chlorazene** has a moderate germicidal value. **Potassium mercuric iodide** has a high germicidal value against the gonococcus. The gonococcus was found to be many times more susceptible to the drugs tested than *B. coli* and *Staphylococcus aureus*.

Lévy-Weissmann (1921) gave a course of ten intramuscular injections of **arsenical treatment** in six cases of gonorrhœa, in addition to the usual local treatment. He believes that the arsenical injections materially shortened the course of the disease.

Martin (1921) has found that an obscure gonococcal infection of the kidney is more

common than is generally supposed, and that direct medication with a 1 in 500 to 1 in 100 solution of **silver nitrate** often cures a gonococcal pyelitis of long standing. In four such cases four instillations of silver nitrate permanently eradicated the gonococcus. This treatment is not so successful, however, where there is a mixed infection.

In gonorrhœal rheumatism he thinks that the best results are obtained by the intravenous injection of 1 in 1000 **perchloride of mercury** according to Baccelli's method of treating acute polyarticular rheumatism. He states that it is so effectual in the cure of gonococcal arthritis that he is amazed that it is not adopted as the routine treatment in every case.

THE AUTHOR'S EXPERIMENTS WITH ANTISEPTICS

Different strengths of various antiseptics (1 c.c. each) were placed in test-tubes with glass beads. One drop of live gonococcal emulsion was added, and after shaking for one minute a small portion was inoculated on to a good culture medium. Where no growth appeared it was concluded that the gonococci had been killed by the one minute exposure to the antiseptic. By numerous experiments carried out in this manner, the weakest dilutions of an antiseptic necessary to kill the gonococcus in one minute were ascertained.

The results were as follows :—

Chemical.	Lowest Dilution necessary to kill the Gonococcus in one minute.
Potassium permanganate	1 in 15,000
Sodium hydroxide	1 „ 1,500
Potassium permanganate	1 „ 20,000
+ Sodium hydroxide	+ 1 „ 2,500
Acriflavine	1 „ 70,000
Picric acid	1 „ 1,800

Further Experiments and Observations.—When saturated picric acid solution is added to an albuminous fluid a heavy precipitate is produced. Concentrated solutions of acriflavine act in a similar manner. On the other hand, very weak solutions of these substances show no precipitating power whatsoever. After observing this phenomenon it occurred to the writer that it would be unwise to use an antiseptic irrigation of such concentration that it would be capable of coagulating the protoplasm of the tissues. Such precipitation would be doubly bad, because in the first place it would be bound to damage the mucous membrane, and in the second place it would retard the penetrative power of the antiseptic itself.

In consequence the following series of tests were carried out in order to ascertain at what concentration a given antiseptic commenced to precipitate albumins.

The following results were obtained with acriflavine and picric acid when added to slightly acid or neutral albuminous fluid :—

Antiseptic.	Strength.	Result.
Acriflavine	1 in 10,000	No precipitate.
„	1 „ 2,400	„ „
„	1 „ 2,000	Faint precipitate.
„	1 „ 1,000	Some precipitation.
„	1 „ 500	Marked precipitation.
„	1 „ 200	Heavy precipitate.
Picric acid	1 „ 1,000	No precipitate.
„	1 „ 900	Faint precipitate.

One would naturally conclude from these experiments that acriflavine should not be used for irrigation in a concentration greater than 1 in 2400. Indeed it would be wise to use it even weaker than this, in view of the fact that it is lethal to the gonococcus in one minute when used in a dilution of 1 in 70,000. A solution, say 1 in 10,000, would be amply strong to kill the germs; moreover, it would not damage the tissues, and it would be likely to penetrate more deeply. Concentrated antiseptics should only be used when it is desired to coagulate the too exuberant granulation tissue of an ulcer or a denuded tissue. Thus it is useful at times to cauterise a follicle with "blue-stone" or "silver stick."

Again, certain antiseptics, such as sodium hydroxide and in fact all the alkalis, have a solvent instead of a precipitating action on protoplasm and albumin. Thus sodium hydroxide, when used in a strength of about 1 in 200, is capable of completely dissolving pus, mucus, epithelial cells and gonococci. If used in such a strength as a urethral irrigation it would dissolve and clear away all the mucus, pus and gonococci, but it would also damage the epithelial lining. Even when used at a strength of 1 in 1000 it tends to render the mucous membrane sodden. If used, however, in a dilution of 1 in 10,000 it forms a non-irritating and very useful irrigation, because it is still capable of cleansing the surface of the urethra, by dissolving away the pus and mucus without in any way damaging the epithelial lining.

It is undoubtedly sound practice to use an irrigation in gonorrhœa composed of a weak antiseptic combined with a weak alkali, or else to irrigate first with the alkali and then to follow up with the antiseptic, which would necessarily act better when the mucus and pus were dissolved away. Dr. Lees has found that this procedure is very efficient and gives excellent clinical results.

Observations on the Bile Salts.—Glycocholate and taurocholate of soda. It was found that both salts were definitely alkaline in 5 per cent solutions, and that they dissolve the gonococcus. This solvent power is no doubt largely due to the alkalinity, and helps to explain why these salts have a beneficial effect on gonorrhœa when injected into the urethra.

Observations on Acid Reactions.—Finger, in his text-book on gonorrhœa and its complications, maintained that a slightly alkaline medium was the most suitable for the development of micro-organisms, and in particular of the gonococcus. He stated that under ordinary circumstances the urethra is bathed in an acid medium, owing to the urine. This slight acidity compromises the vitality of the spermatozoa, but is neutralised by the urethral gland secretion during the orgasm, and this alkaline secretion renders also the urethral mucosa more apt to be infected by the gonococcus.

The writer is in disagreement with the above statements by Finger, and believes that they are erroneous. In the first place, it is now admitted by practically all bacteriologists that the optimum reaction for bacteria, and more especially for the gonococcus, is about +6 to +10 acid to phenolphthalein (Eyre's scale). Plus 6 acid to phenolphthalein is nearly neutral, and corresponds to a hydrogen-ion concentration of about p_H 7.3, which corresponds to the neutral reaction of the blood serum. The writer has found that the gonococcus can grow in a culture medium up to +20 acid to phenolphthalein, but that it refuses to grow on a medium which is definitely but faintly alkaline, because the definite alkalinity dissolves or autolyses the germ. Of course, too much acidity is inimical to all germs, including the gonococcus, but it is doubtful if the urine is ever really sufficiently acid to be able to exert a definite harmful effect on the gonococcus.

Experiments with Antiseptic Ointments. At the Military Hospital, Rochester Row, S.W., several experiments were carried out with regard to the antiseptic power of various ointments with a view to ascertaining which would be most suitable for use in the prophylaxis against gonorrhœa.

In the first series of tests a drop of each ointment was mixed with a loopful of pure gonococci from a culture. After mixing up the germs with the ointment for one minute

in a sterile watch-glass, a small portion of the mixture was inoculated on to a good culture medium.

The results obtained in this series of tests were as follows :—

Ointment Used.	Result of Inoculation after one minute exposure to the Ointment.
Mercury oleate 10 per cent)	No growth after six days' incubation.
+ Neo-Kharsivan (toxic) 1 ")	
Hydrarg. oxycyanide grs. 1½)	Slight growth after one day.
Lanolin ozs. vi.)	
Vaseline ozs. iii.)	Marked growth of gonococci on the second day.
Camphor 2 parts)	
Acid carbolic 3 ")	Fair growth after one day.
Lanolin 15 ")	
Adeps 50 ")	Marked growth on the second day.
2·5 per cent thymol in lanolin)	
Lanolin alone)	Pretty copious growth on second day.
E.T. ointment (33 per cent calomel))	
E.T. ointment, plus 2·5 per cent thymol in lanolin)	Considerable growth after one day.
Colloidal mercury oleate 20 per cent)	
Arsenious acid 5 ")	No growth after six days' incubation.
Ordinary soft soap (Sapo Mollis, B.P.) definitely alkaline)	
Mercury oleate 10 per cent)	No growth after six days' incubation.
Neo-Kharsivan 1 ")	
Mercury oleate alone 10 per cent)	No growth after six days.
Mercury oleate 10 ")	
Neo-Kharsivan 1 ")	No growth after six days.
diluted 1 in 4 with lanolin)	

It will be observed that the arsenic and mercury ointments were the most potent, and appeared to kill the gonococcus in one minute. It is very interesting to note that ordinary soft soap alone had the same lethal effect, no doubt due to its alkalinity. Obviously, therefore, the importance of washing with ordinary soap and water must not be forgotten as a potent factor in successful prophylaxis.

The above series of tests may perhaps be somewhat fallacious, since the ointments in question were always mixed with pure gonococci. In the natural state of affairs the infective material consists of gonococci mixed up with pus cells, and it is just possible that the purulent matter may act as a protection to the germs against the antiseptic ointment.

In consequence another experimental series was carried out in which the ointments were mixed with gonococcal pus for one minute and culture-tubes inoculated as before. In some cases the pus contained secondary organisms as well as gonococci, and they seemed to be more resistant than the latter.

The results were as follows :—

Ointment Used.	Result of Inoculation after one minute Contact with Infective Pus.
Control (no ointment used)	Pus gave colonies of gonococci and diphtheroids.
E.T. ointment (33 per cent calomel)	Diphtheroid colonies but no gonococci.
Hydrarg. oxycyanide	Diphtheroid colonies but no gonococci.
Mercury oleate plus Neo-Kharsivan	A few diphtheroid colonies but no gonococci.
Sapo Mollis	No diphtheroid colonies and no gonococci.

TREATMENT OF GONORRHOEA BY CHEMICALS ACTING THROUGH THE BLOOD STREAM

Numerous drugs have been recommended in the treatment of gonorrhœa, and are administered orally, with the idea that they act on the disease through the blood stream or through the urine.

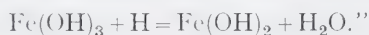
Thus we have **sandalwood oil** and its various derivatives, also **copaiba** and **urotropin**, all of which are supposed to act beneficially through the urine. To these we may add alkaline drugs such as sodium bicarbonate and citrates, which render the urine alkaline. Sandalwood oil, copaiba, etc., have more or less gone out of use, as careful experiments in recent times have shown that they have no marked beneficial effect on the disease. The **alkalis** are still recommended as of some value.

Finally, there have come into use in more recent times quite a series of drugs which are supposed to act through the blood stream, and which are administered by intramuscular or subcutaneous injection.

Thus Hadén (1913) recommended **colloidal sulphur** in solution (1 to 4 per cent) as a good anti-gonococcal substance for injection. He also used it as an irrigation in a strength of 1 per cent.

Fürth (1913) maintained that intra-gluteal injections of "**electrargol**" formed a valuable remedy in gonorrhœal epididymitis, and that this treatment considerably shortened the duration of this complication.

J. E. R. McDonagh (1916-19) may be regarded as one of the chief exponents in the chemo-therapy of gonorrhœa through the blood stream. His ideas as to the action of the various colloidal chemicals (principally metals) are based on a theory of oxidation and reduction. He states that "infection is a battle between the host and the organism invading it; therefore there are two sides which require investigation. The organism (germ) is a mass of colloidal particles enclosed in a fixed area. For maintenance it is dependent upon oxygen, which it strives to gain and protect, and of which when deprived it dies. The protective substance of the host, *i.e.* the material employed to fight the organism, is the blood serum, which consists of colloidal particles moving about in a fluid medium which is on the alkaline side of neutrality. The fight between the organism and protective substance is one fought on the surface of the colloidal particles for the main oxygen supply. The oxygen referred to exists probably in the form of hydroxyl (OH), which has a negative electric charge, and is alkaline. The formation and regulation of this oxygen is dependent on metals, especially those which are capable of existing in two easily reversible hydroxide forms. The chief metal which regulates oxidation in animal life is iron, and in vegetable life manganese. Both these metals can exist as (OH)₂ and (OH)₃, the latter being changed to the former by the action of hydrogen :



It is now generally recognised that acidity depends on the concentration of hydrogen ions, which have a positive electric charge, whereas alkalinity is due to hydroxyl ions (OH), which have a negative electric charge. The hydrogen-ion concentration of the blood serum is estimated to be $p_{\text{H}} = 7.3$, which, as McDonagh states, is on the alkaline side of neutrality.

McDonagh correctly states that every colloidal system contains two electric charges, the positive charge being borne by the hydrogen ions, an excess of which makes the blood too acid and reduces oxygenation. He maintains that the formation and regulation of hydrogen ions is dependent on non-metals, especially sulphur, existing as a sulphide (S₂), whereas the formation and regulation of the hydroxyl ions depend on metals such as iron (Fe) in the case of animals, and manganese (Mn) in the case of plants.

Thus $\text{S}_2 + 2\text{H.OH} = \text{S} + \text{SH} + \text{HO.OH} + \text{H}'$ (hydrogen ion) and $\text{Fe}(\text{OH})_2 + \text{HO.OH} + \text{H.OH} = \text{Fe}(\text{OH})_3 + \text{H}_2\text{O} + \text{OH}'$ (hydroxyl ion). He further asserts that the organism

(germ) to protect its oxygen exhibits on its surface a prevailing positive charge, *i.e.* there is an excess of H' over OH . When the organism gets into the host, the question whether it can become implanted and cause an infection or not depends for one thing upon the OH or negative charge of the serum. If the charge (of the serum) is normal or has excess of OH , the hydrogen on the parasite becomes neutralised and rendered inactive. If this occurs the germ is capable of attracting further OH ions to its surface and so cannot acquire active oxygen by converting its $Mn(OH)_2$ into $Mn(OH)_3$, so that it may die from lack of oxygen. If, on the other hand, the OH ions in the serum are below normal, the attracting H' ions on the surface of the colloid particles of the germ will not be wholly neutralised, with the result that the germ will be able to seize oxygen (OH ions) and hence thrive and live, and so cause an infection of the host. Once the germ has become implanted, the host not only attempts to increase its oxygen, but also to build up its colloid particles in a form resembling the colloidal particles of the organisms. The object of the latter action is to increase the surface reaction (adsorption), and so the battle is intensified. He holds that the amount of oxygen (hydroxyl ions) in the serum can be increased by the administration of metals, and the surface action is increased by administering the metal in colloidal form. Further, he maintains that if the drug is used in the colloidal form, or has an amino-group (NH_2) in its molecule, such as arsenobenzene, or has a high atomic weight, such as mercury, it breaks up the colloidal particles in the serum into several smaller ones. This has the result of increasing the area of the surface exposed to the parasite. Finally, he states that drugs are not specific, but act only indirectly by increasing the action of the host's protective substance. Small doses of metals, according to McDonagh, increase the amount of oxygen in the serum, but overdoses produce the opposite effect by using up the available peroxide and by becoming themselves oxidised. The antidotes to this action are **colloidal iodine**, which acts indirectly, or **intramine**, which acts directly in producing more peroxide.

The dosage of these drugs is important. Over-large doses are harmful; thus overdoses of metals such as arsenic or mercury render the blood too acid (the hydrogen-ion concentration becoming too high) and thereby cause dermatitis, stomatitis, etc. In such conditions one should give a colloidal non-metal, such as intramine (a sulphur compound), or colloidal iodine, which are reducing agents and render the blood more alkaline (richer in hydroxyl ions). On the other hand, overdoses of the non-metals such as sulphur are also capable of producing dermatitis and eczematous conditions by rendering the blood too alkaline. The antidotes in such cases are metals such as arsenic or, better, colloidal manganese.

According to McDonagh, therefore, the dosage of his colloidal preparations is very important. He has recommended for the treatment of gonorrhœa injections of **colloidal manganese**, also **pallamine** (colloidal palladium), and **trimine** (a mixture of iron, manganese and zinc). He has found that an overdose of certain of these colloidal metals may precipitate an attack of epididymitis or gonorrhœal rheumatism, so care must be taken.

Intramine (sulphur compound) he declares is a specific for gonorrhœal rheumatism.

Although the various workers on the subject do not see eye to eye with McDonagh's theories, and although some clinicians have failed to obtain the good results claimed in the case of these new preparations, nevertheless one cannot deny that this colloid hypothesis of oxidation and reduction is very fascinating and ingenious.

It is very difficult clearly to grasp this hypothesis, and still more difficult to prove its correctness experimentally. Very accurate apparatus would require to be devised for this purpose. McDonagh maintains that germs exhibit hydrogen ions on their surface in order to attract oxygen (OH) ions. This would appear to be contradictory to experimental facts. Most germs are considered to be negatively charged, since, under the influence of an electric current, they travel towards the anode or positive pole. This would indicate that they would exhibit negative or hydroxyl (OH) ions on their surface. It is in virtue of this negative charge that they repel each other and do not agglutinate in spite of surface

tension. When, however, a fairly strong solution of NaCl or CaCl_2 is added to an emulsion of germs they agglutinate. It is believed that this agglutination is caused in the following manner :—

(1) These salts are charged with hydrogen ions which neutralise the hydroxyl ions on the surface of the germs.

(2) The charge on the germs having been neutralised, they no longer repel each other, and they agglutinate together under the laws of surface tension.

Agglutination of germs, however, as it occurs in nature under the influence of specific agglutinins formed in the blood is not such a simple matter as the above. It is no doubt due to the electrical charge of colloid particles, but there are apparently complications the nature of which is so far little known. The writer's experiments have shown that autolysed colloidal solutions of gonococci are precipitated by the addition of weak acids, *i.e.* by increasing the hydrogen-ion concentration of the solution ; this would appear to indicate that the colloidal particles of autolysed gonococci are negatively charged.

The author does not feel in a position to criticise the oxidation and reduction hypothesis, as he has not so far carried out sufficient experimental work on similar lines. There can be no doubt, however, that all researches on the colloidal chemistry and the electro-physics of germs and of the body fluids are of the greatest importance, but whether pure metals in colloidal form are better as therapeutic agents than molecular solutions of salts of the same metals is still very hard to decide. McDonagh, however, whether he is right or wrong, is to be congratulated on the amount of work he has done on this subject, which is a very important line of research and requires much further elucidation.

Fraser (1922) makes the following observations on the chemo-therapy of gonorrhœa :—

"Many haphazard efforts have been made to deal with the acute urethritis of gonorrhœa by injecting various chemo-therapeutic drugs into the general circulation. Mercury is known to have a certain faculty of stimulating the production of immune bodies in syphilis, and possibly for this reason was the drug most frequently tried. There was, however, no serious well-considered plan of procedure, and no theoretical hypothesis on which to build. The results therefore were uncertain and usually disappointing.

"**Succinamide of mercury** in 0.5 gramme doses given intramuscularly every fourth day was tried for no particular reason. In a great many cases it caused a great deal of pain, and the reasons why in some cases it seemed to affect the discharge while in others it did not were not understood. Possibly an increased leucocytosis had something to do with it, but this is an uncertain factor on which to depend for therapeutic efficiency. Other salts used from time to time were the **benzoate**, **phthalamide**, **bibromurate**, and **salicyl arsenate**.

"Intravenous therapy has been tried experimentally, chiefly in the complications of gonorrhœa. **Collargol** and **electrargol** have been reported on favourably, but results have been uncertain. This has been the experience of Menzi and of Romeick, who recommend that this procedure should only be tried in robust cases which can be closely watched. Severe headache and albuminuria are apt to occur, even after 2 c.c. doses of a 2 per cent solution. Bruck reports favourably on **trypaflavine** in epididymitis. He employed a dose of 50 c.c. of a 0.5 per cent solution. In gonococcal septicæmia Bohland, Mergelsberg, and also Ahlswede have noted good results. **Sanoflavine** and **argochrom** (methylene blue and silver) gave uncertain results in the hands of Bruck, but more success attended the efforts of Ahlswede and Patschke with **argoflavine**. The effect on the acute urethral condition was uncertain, and the influence on the gonococci appeared negative. There was an excellent effect on gonococcal septicæmia, arthritis and teno-synovitis.

"Much advance in the chemo-therapeutic treatment of gonorrhœa we owe to the work of McDonagh, who, working along the lines of his 'Theory of Oxidation and Reduction,' sought to establish its confirmation by evolving a therapeutic procedure from a chemo-therapeutic standpoint. His main object is to regulate oxidation over a large area, and for this purpose metals in colloidal form are employed. The obvious risk is that the

metal itself may become oxidised, and this risk is a real one in such a disease as gonorrhœa, where the infection is purely local. In the early stages of the urethritis, then, it is a safer plan to employ a non-oxidisable metal such as palladium. Other valuable colloids are manganese, antimony, vanadium, sulphur (intramine), and ferro-manganese zinc (trimine).

"Many schemes of treatment have been advocated both as regards the metal employed and the size and frequency of the doses. So far the following plan seems to promise the best results, but each case must be treated on its merits, and such signs as temperature, amount and nature of discharge, reaction of urine, and so on, fully considered. **Colloidal palladium** is given intramuscularly on the first day in a dose of 1 c.c. At no subsequent date is palladium employed. It is merely used as an initial injection on account of the fact that it is a non-oxidisable metal. Four days later 0.5 c.c. **colloidal manganese** is given intramuscularly, and repeated every four days until the discharge disappears. The dose may be increased to 1 c.c. if desired. **Trimine** may replace the colloidal manganese in doses of 0.5 to 1.5 c.c., often with advantage. Should the case run a chronic course, however, **intramine** in doses of 2.5 to 5 c.c. should gradually take the place of manganese or trimine.

"The internal administration of sodium bicarbonate and potassium nitrate in large doses assists, rather than retards, the action of these chemo-therapeutic agents. These agents should not be considered as an alternative to correct local treatment. On the contrary, they are essentially auxiliaries, and should be employed in much the same spirit as vaccines.

"Many disappointments have been met with, but occasional startling results have served to maintain one's interest. McDonagh believes that much of the failure is due to the intracellular life of the gonococcus, together with the fact that in the early stages the disease is a purely local one, and the call for *protective substances* is never very urgent. The first is probably the more important factor. Indeed, the success obtained with detoxicated vaccines would seem to negative the latter.

"In the complications of gonorrhœa, however, the value of trimine and intramine is very striking. In no type of case is this more marked than in gonococcal arthritis. Their routine inclusion in the treatment of this condition is already well recognised, and their exclusion quite unjustifiable. In acute prostatitis, vesiculitis, epididymitis, and in gonococcal skin affections, trimine and intramine therapy should always be employed, not necessarily as an alternative, but certainly as an adjuvant, to other therapeutic procedures.

"While recognising that the application of the 'Theory of Oxidation and Reduction' is essentially in the experimental stage, and in many quarters has been condemned *in toto*, one must confess that results sufficiently striking have been obtained to justify one in developing treatment measures along the lines indicated. By closely following the principles laid down by McDonagh, one finds that much of what is claimed for the success of treatment is realised. Should future research perfect chemo-therapeutic drugs, local treatment will assume only secondary importance, and in dealing with the disease entirely *via* the blood stream a vast field will be opened up—in the male who finds it essential to conceal his treatment outfit, and in the female where the possibility of local treatment is so limited."

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CHAPTER XXXV

ELECTROTHERAPY AND THERMO-THERAPY IN GONORRHOEA

ELECTROLYSIS ; HIGH-FREQUENCY CURRENTS ; DIATHERMY ; ULTRA-VIOLET RAYS ;
HOT BATH TREATMENT

THE treatment of acute gonorrhœa by **electrolysis** has been evolved by Russ, and in his hands it has given apparently excellent results. The rationale of his procedure depends on the fact that micro-organisms suspended in saline solution in a U-tube fitted with electrodes will steadily migrate to the positive pole when the current is running. In addition to this migration, the organisms soon die after the current is turned on. With these data, then, it seemed reasonable to conclude that if the affected urethra were bathed in saline and a current passed through it, the organisms would be drawn to the surface and killed.

Treatment of gonorrhœa by employing **high-frequency currents** has been advocated in America. The apparatus required is considerable, and, even on a small scale, expensive. A high-frequency apparatus of the Tesla or D'Arsonval type is essential, and portable coils are available.

A glass electrode is passed into the urethra and run off the Tesla side of a high-frequency transformer. The action of the current is to liberate, from the small amount of air around the glass electrode, ozone which has high bactericidal properties. The violet light has also similar properties. As a rule, however, the urethra is too sensitive to tolerate the vacuum tube.

An alternative procedure adopted by Snow and by Eberhart is to surround the penis with tinfoil protected with wet gauze, and connect it to the D'Arsonval bi-polarity current (to all intents and purposes the diathermy current), the second electrode being in the rectum.

A third method is to apply a metal plate over the penis and a vacuum electrode in the rectum. In this way the sensitiveness of the urethra need not be considered.

According to Fraser (1922) there is little doubt that the increased local leucocytosis established is beneficial, but possibly the important factor is the bactericidal action of the violet-rays and of the ozone liberated.

Gibson (1916) tried the electrolysis treatment as advocated by Russ in 17 cases of early gonorrhœa. He was not impressed by the results, and considers it is bad practice to introduce any kind of instrument into an acutely inflamed and purulent urethra unless absolutely necessary.

The cases which he tried had passed the acute purulent stage. Out of the 17 cases 3 showed no gonococci in the urine after treatment, and were dry. In 7 cases, 41·2 per cent, he stopped the treatment because of threatened or commencing complications. Three cases complained of acute pain or marked soreness after electrolysis. Three cases developed hæmorrhage or hæmaturia after it, and one case developed orchitis.

No improvement was noticed except in the 3 cases which finally showed no gonococci, and these were well on the way to cure when the treatment was tried.

Lumb (1917) was unable to find any curative effect with the electrolysis treatment.

McDonagh (1920) states that in his experience the electrolysis treatment of Russ is most useful in subacute cases of folliculitis and perifolliculitis which have resisted other methods. In acute cases, however, it is too apt to cause an extension and aggravation of the disease, and it takes up too much time to be generally utilised. He thinks it is possible that better results might be obtained if a weaker current were used and a non-irritative solution employed.

Another application of electrical treatment is by **diathermy**. The gonococcus is very easily killed by temperatures over about 42°C . The idea of diathermy is therefore to raise the temperature of the urethra and the surrounding tissues above 42°C . by means of an electrically controlled bougie. Harrison and others have not been impressed favourably by this form of treatment.

The drawback of all these methods of treatment is, as Gibson points out, the undesirability of introducing an instrument into an acutely inflamed urethra. Again, neither the diathermy nor the electrolysis nor the violet-rays are capable of getting at the gonococci lying deeply situated—in the prostate, for example.

Canovas (1918) reported favourable results in cases treated with from 5 to 30 applications of diathermy. He obtained cures in various patients who had had gonorrhœa of one week to three years' duration. A case of gonococcus prostatitis was amongst the cured cases, and only one patient showed no benefit from this form of treatment.

Martin (1921) reports that diathermy is very successful in the treatment of gonococcal epididymitis. He states that the effect of the heat is indirect, and that the germs are not actually killed by it. The curative effect is due to the fact that the tissues are stimulated to active defence by the heat.

Moore (1918) recommends the **electric cautery** in the treatment of chronic gonorrhœal Skenitis.

The author has recently carried out experiments with the **Paschler ultra-violet lamp**. It was found that the rays of this lamp killed staphylococci directly exposed on a Petri dish after five minutes' exposure. The rays had no killing effect, however, through even a thin sheet of glass or paper. Any ultra-violet apparatus introduced into the urethra must therefore be made of quartz. Experiments showed that the killing effect of the ultra-violet rays on germs was apparently due to the formation of nascent ozone in the path of these rays.

The production of ozone was estimated by means of paper and solutions saturated with potassium iodide and starch. After the rays had passed through a sheet of glass their ozone-producing power was almost entirely destroyed. They could, however, pass through six inches of quartz and still produce abundance of ozone after emerging from the quartz rod. The rays were directed into the open end of a test-tube containing agar impregnated with potassium iodide and starch, and they immediately produced a blue colour on the surface, indicating ozone. When the layer of agar was covered with one inch of water, the rays were capable of penetrating the water and producing ozone at the junction of the water and agar layers. No ozone was produced, however, by the rays after they had penetrated a half-inch layer of liquid paraffin or of agar.

These experiments show that there is little hope of the rays penetrating deeply into the tissues and exerting their action there. They may, however, exert a curative effect in the deeper layers through absorption, or by producing a reaction in the living tissues.

Thermo-Therapy.—Ylppö (1916) describes a case of gonorrhœal vulvo-vaginitis in a child of five years which he treated successfully by heat treatment. The child was placed in a bath tub with the water at 102°F . extending up to the umbilicus. Hotter water was then gradually added until the temperature reached 105° to 107°F . and the level of the water was raised till it reached the nipples. This heat treatment was applied for one hour daily for eight days, after which no gonococci could be detected. The treatment was

continued for a second week. This treatment is based on the fact that the gonococcus is easily killed by temperatures of about 41° to 42° C., *i.e.* 105° to 107° F.

Kapferer (1920) found the Weisz method of treatment (hot-bath treatment) very weakening to the patients, and on this account some of them were obliged to discontinue it. The aim is to kill the gonococcus by raising the temperature of the body to 40° C. or over, and to keep it at this point. The temperature of the bath is raised within fifteen minutes from 38° C. to 43° or 45° C., and if possible to 46° C., *i.e.* 114.8° F. Kapferer, however, found that the curative effect was very uncertain, and the method has the disadvantage that it requires the constant presence of a physician or nurse.

Schwarz (1920) also discusses the Weisz mode of treatment, and states that the prolonged hot bath is well borne by carefully selected patients. He states that Scholtz and Dinker obtained good results with hip baths, when such treatment was combined with the usual irrigation treatment. Others have reported untoward effects of the high temperatures, especially in children.

The application of curative heat has been used in the Budapest Polyclinic since 1918. Instead of baths, however, hot irrigations are used. The value of the antiseptic irrigation is stated to be greatly enhanced by heating the fluid to 39° C. to 43° C., *i.e.* 102.2° F. to 108° F. No untoward consequences have followed this treatment.

Büben (1921) reports that although every case cannot be cured by thermo-therapy, nevertheless in a number of cases of gonorrhœa this mode of treatment succeeded after various other methods had failed.

Langer (1922) allows patients with gonococcal arthritis to exercise their joints actively in a full hot bath. They are then given a hot-air bath. In severer cases, however, the joints are kept at rest in splints. He considers that vaccine and protein therapy are invaluable adjuvants to this form of treatment.

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PART V

PROPHYLAXIS AND ABORTIVE TREATMENT

CHAPTER XXXVI

THE MENACE OF GONORRHŒA AS A NATIONAL CONTAGIOUS DISEASE, AND THE PROBLEM OF ITS PREVENTION

MENACE OF GONORRHŒA: PREVALENCE IN MEN AND WOMEN; PREVALENCE OF COMPLICATIONS; FREQUENCY OF BLINDNESS; UNHAPPY MARRIED LIFE AND STERILITY; IS GONORRHŒA INCREASING OR DECREASING? THE OUTLOOK FOR THE FUTURE; METHODS OF COMBATING THE DISEASE: RELIGIOUS INSTRUCTION; PREACHING OF MORALITY; LEGISLATIVE PROCEDURES; NATIONAL COUNCIL FOR COMBATING VENEREAL DISEASES; SOCIETY FOR THE PREVENTION OF VENEREAL DISEASES; ARGUMENTS AGAINST THE TEACHING OF VENEREAL PROPHYLAXIS; CONCLUSIONS REGARDING THE CORRECT MORAL VIEW; CONCLUSIONS REGARDING THE CORRECT SCIENTIFIC VIEW

The Menace of Gonorrhœa.—Gonorrhœa is a contagious disease of the greatest national importance because of its wide and constant prevalence in the human race in every part of the world. It is a menace not only on account of this extraordinary prevalence, but also because its effects in many individuals may be far-reaching and disastrous. It is well known that gonorrhœa is one of the most important causes of blindness in the world. It is the chief cause of sterility in both the male and the female, and it is the cause of at least 50 per cent of the total gynæcological complaints from which women suffer.

The dangerous and far-reaching effects of gonorrhœa are due to the fact that numerous local complications such as prostatitis, epididymitis, cervicitis, metritis, salpingitis and ovaritis are very common. Even metastatic complications in the remotest parts of the body, such as arthritis, iritis, endocarditis, etc., are by no means rare.

The serious menace of this disease is further increased because of the great difficulty in curing many cases, and because of the long infectivity of the complaint, more especially in women.

The Prevalence of Gonorrhœa. Exact figures on the prevalence and spread of gonorrhœa are very difficult to obtain, because it varies to some extent amongst different peoples and different classes of society, and also because it is not notifiable. Further, it is a disease which the patient attempts to keep secret even from his own physician. The sufferers as a rule prefer to go for treatment to some clinic or doctor in a town where they are unknown.

Erb (1906-7) attempted to estimate the prevalence of the disease in Germany, and he compiled statistics from 2000 cases in his own private practice, which included persons from the highest ranks of society, both civil and military, as well as from the middle classes and the peasantry. From his investigations he concluded that about 50 per cent of his patients had suffered from gonorrhœa at some period of their life. He was unable,

however, to confirm the exaggerated statements of other observers who declared that more than 80 per cent of the population had had the disease.

With regard to the **age incidence** of gonorrhoea, Erb found that out of 386 married men who had suffered from the disease, by far the greater proportion (almost 85 per cent) had been infected before the age of twenty-five years. About 11·5 per cent acquired it between the ages of twenty-six and thirty years, and scarcely 4 per cent contracted it beyond the age of thirty.

Erb's figures as to the prevalence of gonorrhoea have been strongly contested by Blaschko (1907), as well as by Neisser and others.

According to Neisser's statistics, which were compiled from the whole civil population of Breslau, the number of gonorrhoeal patients during the year 1896 amounted to 9 per 1000 of the total number of inhabitants. This number, however, according to the opinion of Neisser and Scholtz (1903), falls far short of the actual figure, since a large proportion of the patients did not come under the observation of the physicians, and according to the statement of the statistics only about 80 per cent of the physicians in Breslau had participated in giving records.

J. Koch (1912) states that the number of cases of gonorrhoea which occurred in the German army each year amounted to 15 to 17 per 1000 officers and men. In the Austrian and French armies it was even as high as 3 per cent per annum. From the statistics of isolated sick clubs it was estimated that amongst students, tradespeople and other classes the disease was present in from 10 to 25 per cent.

Koch points out that it is very difficult to obtain an accurate conception as to the prevalence of gonorrhoea in the female sex, because in recent cases in women the symptoms may be so trifling that the disease is often overlooked, and for this reason such cases, although highly infectious, remain untreated. Further, in the chronic stages of the disease in women it is extremely difficult even for the specialist to give a definite positive diagnosis. Koch believes, therefore, that the most reliable information as to the extent of the disease in women may be obtained by estimating the prevalence of gonorrhoeal ophthalmia in newly-born infants. The statistics from various maternity hospitals in Germany show that prior to the introduction of Credé's methods of preventing eye infection, ophthalmia neonatorum occurred in 10 to 14 per cent of the children born, and this naturally indicates that at least 10 to 14 per cent of the mothers suffered from gonorrhoea. In these maternity hospitals the pregnant women came partly from the labouring classes, and included many who were unmarried. Schwarz estimated that 12·4 per cent of these mothers were infected with the disease, whereas Oppenheimer and Lomer placed the figures as high as 27 and 28 per cent respectively.

Koch further maintains that it is just as difficult to form a true estimate of the **prevalence of gonorrhoeal complications** as it is to gauge the extent of the disease itself. He believes that Neisser's statistics are perhaps the most reliable. This latter observer estimated that 30 per cent of all cases of gonorrhoea developed some local or general complication of the malady. Thus in 10 per cent the bladder was affected. Nineteen per cent showed epididymitis, whilst 1·5 per cent had tubal and ovarian infections, and 0·7 per cent had metastatic complications. The statistics of other more recent authorities differ somewhat from those of Neisser; thus Luys (1917) estimates that gonorrhoeal rheumatism occurs in 2 per cent of all cases. With regard to epididymitis, he places the figure as high as 25 per cent, whilst McDonagh (1920) estimates that it occurs in 15 per cent of all cases in the male, and that vesiculitis is found in 7 per cent.

The frequency of blindness as a result of gonococcal infection of the eyes is recognised as a matter of grave national concern. There is no doubt that blindness is one of the most disastrous consequences of gonorrhoea. It is caused as a result of ulceration of the cornea, producing incurable opacities. In some cases the eyes are entirely destroyed, due to panophthalmia, where the gonorrhoea has spread from the conjunctiva into the tissues of the eyeball itself.

Koch states that before the introduction of Credé's method of prophylaxis against ophthalmia neonatorum, this gonococcal affection of the newly-born was the cause of about 60 per cent of the total blindness in the world. Neisser estimated that in Germany there were about 30,000 cases of blindness which could be traced back to gonorrhœal ophthalmia. Cohn maintained that in 1904, in spite of the general application of Credé's discoveries, still 30 per cent of the blindness in children was due to gonococcal infection of the eyes at birth.

The Prevalence of Unhappy Married Life and Sterility as a Result of Gonorrhœa.—Noeggerath (1872) was the first to point out in a forcible manner the evil consequences of gonorrhœa in women. He drew attention to its disastrous influence in reducing the birth-rate because of its sterilising effect on both sexes. He further showed its far-reaching results in producing chronic ill-health in the wives, results which permanently marred the happiness of married life. He maintained that in New York no less than 800 out of 1000 husbands had suffered from gonorrhœa and that 90 per cent of them had not been cured. Their disease, although it had become latent, remained infectious, and thus nearly all married women were infected!

Koch states that in the beginning of last century the importance of gonorrhœa as a cause of the internal complaints of women was underestimated; later, however, as a result of Noeggerath's teaching, it was inclined to be exaggerated.

Von Schaick (1897) carried out a systematic research in order to ascertain to what extent married women suffering from leucorrhœa harboured gonococci. He found that the gonococcus was present in 26 per cent of 65 such cases examined in the course of three years.

Schaper (1899) collected statistics from one of the German hospitals which showed that the number of gonorrhœal patients in the surgical division fluctuated between 3 and 20 per cent. In the gynæcological department, on the other hand, the figure sometimes exceeded 30 per cent. He found that the complications of gonorrhœa which required surgical operations had quite a serious influence on the death statistics of the hospital.

Luys (1917) emphasises the dangers of gonorrhœa very forcibly, and draws attention to its evil consequences in affecting the happiness of married people. He says: "*How often do we not hear this doleful statement repeated by young wives—As a girl I was very strong and well; since my marriage my health has left me.*" An alarmingly great number of young women are confined for months or even years to their bed or their sofa, and pass their days in worrying over their shattered health. The gravity of their lesions condemns them to resort to all sorts of precautions with which they manage to continue a life of misery for some time, but their only hope of cure is a serious operation which deprives them of their diseased organs and renders them sterile for ever.

"And those who suffer thus are not only prostitutes and ladies of easy virtue who, as Verchère puts it, merely run the risks of the trade, but also married women who are absolutely straight and faithful and have nothing to reproach themselves for except a mistake in the choice of their husbands. One cannot close one's eyes to the fact that very often the parents are guilty of negligence or ignorance in these instances, and that unfortunately also the medical adviser is not always free from the blame of having reported favourably on the *fiancé's* health without having examined him with sufficient care."

Further information with regard to the seriousness of gonorrhœa as a cause of pelvic inflammatory ailments in women, and as a cause of sterility and blindness, will be found in Chapter XVII., pp. 146-150.

Is Gonorrhœa Increasing or Decreasing?—It is interesting to speculate as to whether gonorrhœa is more prevalent to-day than it was in ancient and medieval times.

It is highly probable that in remote agricultural populations some hundred years ago, before the discovery and development of the steamship and the railway train, the disease was comparatively rare, but that like most other infectious diseases its opportunities for spreading increased as the facilities for trade penetration and travel into the furthest parts of the world developed. There can be little doubt that in modern times, say during

the last fifty years, the disease has become much more prevalent and widely spread than it ever was before in the history of the world. This is due to several factors, such as the increased intercommunication between the different populations in all parts of the world, the rise and growth of towns, the influx of millions of young men and women into these cities, seeking employment away from the influence of home life, the constant travel between town and country, and the effect of civilisation in deferring the opportunity of marriage at an early age.

It is generally agreed amongst venereal disease experts in this country that the high-water mark of the prevalence of gonorrhœa and syphilis was reached in Europe, at any rate, towards the end of the Great War, or immediately after it.

During the war there were always some 10,000 cases of venereal disease (chiefly gonorrhœa) in our army hospitals all the year round. If we estimate that one month was the average sojourn of each patient in hospital, this means that there were 120,000 cases per annum. During the five years of the war, therefore, the total number of cases would be over half a million, or about 10 per cent of the whole army of five millions.¹

Immediately after the war the amount of gonorrhœa in the army of the Rhine reached an enormously high figure, due partly no doubt to the fact that there was no fighting and the soldiers had much more leisure, and partly because they were quartered in and near a large town.

There is no doubt that the war did much to increase the spread of gonorrhœa in the civil population as well as in the army. Not only was there an increased prevalence of the disease in towns, but it also spread to the remotest country districts.

The enormous armies recruited during the years 1914-1918 brought hundreds of thousands of young men and women from the remote places of Britain and other parts of the Empire to the large towns. Many became infected with the disease and thereafter returned to the distant places from whence they came, carrying the complaint with them. Gonorrhœa, therefore, which before the war was to a large extent a town disease, became suddenly quite common in the country as well.

The Outlook for the Future.—It is highly probable that the spread of gonorrhœa into remote country districts, which occurred during the war, will die down in a generation and that it will become again for the greater part a disease of towns; nevertheless, it will continue to be more prevalent in the country than it was in the past, due to the ever-increasing facilities of modern transport between the two. With regard to the continued prevalence of the disease in large towns, there is no likelihood of its dying out unless the State takes adequate measures to combat it with all the power of modern scientific knowledge at its command.

It is very unfortunate that an attack of gonorrhœa confers no immunity against further infections. The disease, therefore, unlike most other epidemics, does not tend to die of itself. If allowed to run its natural course the outlook for the future would be exceedingly gloomy. The sense of decency, the morality, the humanity and intelligence of the civilised peoples of to-day are no doubt better developed than ever before, but the temptations and opportunities for promiscuous intercourse between the sexes have multiplied enormously in recent times, especially in all large towns. The mental and moral development has been insufficient to counterbalance these great and sudden changes in civilisation, with the consequence that venereal disease has increased and is likely to continue increasing to an alarming extent, unless a strenuous fight is put up against it. A little knowledge may be a dangerous acquisition, and it would appear that during the past few years it has become common knowledge amongst even the youngest adults of both sexes that conception can be avoided by quite a variety of measures which are apparently simple to carry out. General yet insufficient information of this nature is

¹ Miss Ettie Ront, in her book on *Safe Marriage* (1922), states that "during the war there were half a million fresh infections of venereal disease per annum among the soldiers in the British Armies alone—about two million men infected altogether at the very least."

highly dangerous to the community, since there can be little doubt that it has been the cause of a considerable increase of promiscuous intercourse between the sexes in all classes of society. The author has sufficient faith, however, in the common sense and decency of our modern civilisation, to believe that when the imperfect knowledge so far acquired becomes more profound, as it must in a few more years, the enlightened people will restrain themselves to a considerable extent for their own ultimate happiness and for the good of the State in general.

METHODS OF COMBATING THE DISEASE

Religious Instruction—the Preaching of Morality and Chastity.—There is no shadow of doubt that if every individual in the world obeyed to the letter the Christian teaching of morality and chastity during the whole of their lives, gonorrhœa, which is not a hereditary disease, would disappear from the earth in almost one generation. This teaching, however, has already been carried out persistently for nearly 2000 years, and yet in Christian communities to-day gonorrhœa is more prevalent than it ever was before. It is obvious, therefore, that although the Christian instruction as to chastity is correct to perfection, yet the vast majority of human minds are unfortunately not nearly sufficiently developed to be able to carry such high ideals into practice in daily life. Obedience to the instruction is still for the masses a human impossibility. In another 10,000 years perhaps the masses may be sufficiently advanced in mind and spirit to conform more closely to these ideals; but the sane mind of to-day must admit that the hope of abolishing venereal disease from the world in the near future by religious instruction alone is impracticable for our generation and for many generations to come, and that other methods of prevention are imperatively demanded for the safety and happiness of civilisation.

Legislative Procedures—Control of Prostitutes; Notification, etc.—With regard to other contagious diseases, legislation based upon scientific discoveries and accurate knowledge has been of great value. In the case of venereal disease, however, it would appear that legal measures calculated to help in preventing the spread of the malady are surrounded with extraordinary difficulties. The necessary scientific knowledge is available, but these diseases are so intimately associated with the normal physiological functions of the race that most of the conceivable laws calculated to help in preventing the spread of the malady would cause profound discontent and a great amount of misery. Attempts have been made to abolish prostitution, but this is impossible. **The control of prostitutes** has been accomplished to a certain degree, but the results are more or less negligible so far as the checking of venereal disease is concerned. The great difficulty of controlling prostitution is by no means the principal cause of this failure. It was estimated from careful investigations that in the army during the war, only 20 per cent of the total venereal disease was contracted from prostitutes. If, therefore, all the prostitutes in the world were not only controlled but completely wiped out of existence, yet 80 per cent of the source and spread of the infection, viz. the more or less respectable male and female population, would still remain.

Laws which enforce the **notification and isolation** of certain infectious diseases have been of considerable value in preventing the spread of epidemics, but such legislation is hardly likely to succeed in the case of venereal disease. The patients are ashamed of their complaint. They hide it from their friends and prefer to go to a strange physician or clinic for treatment. Rather than suffer the stigma of uncleanness through compulsory notification and isolation, or of notification alone, those afflicted would hide their complaint to the bitter end. This would mean that large numbers of patients would go untreated, or else they would attempt to treat themselves. Such legislation therefore would defeat its own purpose, and would favour rather than combat the progress of the disease. The wise aim of venereal treatment-centres to-day is to encourage the patients to come

as soon as the complaint has manifested itself, since it is only in very early cases that the disease can be quickly and completely cured. With this end in view the identity of persons attending for treatment is not recorded and remains unknown.

It has been considered that legislation forbidding the sale of anticonceptive devices might reduce the amount of promiscuous copulation, and thereby have an influence in combating the disease. It is almost certain, however, that the result would be negligible. People would resort to other measures perhaps less effective and perhaps more dangerous. In any case there is a certain need for anticonceptives amongst respectable married people. There can be little doubt also that if the population of the world increases at the present rate, legislation would be required within the next few hundred years in order to make the use of anticonceptive devices compulsory. Finally, the situation may be truthfully summed up by stating that all attempts to abolish gonorrhoea from the land by purely religious or legislative methods, separately or together, are doomed to fail, and the more quickly this is realised by every one the better.

With great reluctance, and in spite of numerous protests from religious authorities, the State has at last come to realise more or less clearly the truth of these conclusions. The State has now turned for help to the great store of scientific knowledge on venereal diseases which, thanks to the untiring researches of thousands of medical men, many of whom are mentioned in this book, is now available. The first essential for the successful application of scientific knowledge towards the prevention of a disease is to interest the public and the State. When this has been accomplished it naturally follows that commissions are established to investigate the facts available, and to devise from such information the best methods for combating the scourge concerned. Fortunately, in Great Britain and in many other countries these preliminary stages have already been carried out, and certain measures devised for combating venereal disease are already in operation.

In 1914 the **National Council for Combating Venereal Diseases** (N.C.C.V.D.) was formed in this country, and it has already laid the foundations of success. Through the Ministry of Health it has been the means of establishing *venereal treatment centres* all over Britain. The universities have been stimulated to make venereal disease a compulsory subject in the medical curriculum, and special post-graduate classes have been established for those already qualified. Furthermore, this Council, by means of an extensive and accurate propaganda, is educating the public. This education will be of great value in furthering the development of other schemes which will no doubt be required before we can hope to obliterate the scourge.

The present education of the adult public consists in emphasising the great danger of contracting this prevalent disease through promiscuous copulation and the serious consequences that may arise if it is not thoroughly treated as soon as the first symptoms arise. It is hoped that this widespread instruction, combined with the facilities for thorough early treatment, free of charge and without stigma, in centres all over the country, will enable doctors to tackle the disease in most cases at an early stage, and that on this account the majority of new patients will be rapidly rendered non-infectious and cured. There can be no doubt that the N.C.C.V.D. and the Ministry of Health, working together, have laid the foundation of a work of great value to the health of our population. Their policy, so far as it goes, is sane, practical, and moral. The full scheme has now been in operation since the end of the war, and there is good reason to believe that venereal disease, though still very prevalent, shows some signs of decline. It may be possible, however, that this is a natural fall in the abnormally high wave of incidence which occurred as a result of the war. It is still, indeed, too early to gauge the effect of these important measures.

It will be noted that the N.C.C.V.D. has not attempted to educate the public with regard to self-disinfection immediately following exposure to venereal disease. Its methods, therefore, are not so much preventive as combative, as its name implies.

Many medical men were strongly dissatisfied with this attitude of the National Council in confining its efforts to combating the disease by "fear" propaganda and early treatment, and because it refused to advocate actual measures during or immediately following copulation, which would prevent the disease from settling upon the individuals concerned. About three years ago several of these dissatisfied physicians in conjunction with sympathetic laymen established the **Society for the Prevention of Venereal Diseases**. This society, as its name implies, maintains that "prevention is better than cure," and its supporters believe that the most efficient method of stamping out gonorrhœa and other venereal diseases from civilised populations is to educate the public with regard to certain disinfectant and preventive measures, which should be carried out by the individuals concerned during or immediately after exposure to infection. This society advocates, therefore, that the whole adult population should be educated with regard to methods of antiseptic cleanliness, that posters giving the necessary information should be placed in all public conveniences, that the necessary antiseptics should be supplied by chemists, and that every facility and encouragement should be given for their use. It claims that the disinfecting procedure is simple and efficacious, and well within the comprehension of the average individual.

During the past two years a considerable controversy has arisen between the two societies with regard to this matter. The author will only give a brief outline of the arguments brought forward by either side, but those who wish to study them in greater detail should consult the *British Medical Journal* during the years 1920-22, and more especially the numbers for the year 1922. See also the *Journal of the American Medical Association* (1921), vol. lxxvii. p. 2131.

Some believe that this controversy has done much harm to the cause in general, but in reality it has done much good, since it has brought many intellects to bear upon the subject, and has been the means of stimulating further experiments and of bringing further information to light with regard to the matter.

Recently the N.C.C.V.D. has become inclined to favour the establishment of "ablution centres" in towns, where those who have exposed themselves to venereal infection may come at once and be treated with disinfectant applications by persons specially trained for this work. If this measure is finally adopted, then it has met the Society for the Prevention of Venereal Diseases half way.

The N.C.C.V.D. still holds out firmly, however, against the procedure of broadcasting literature and posters on methods of self-disinfection, and the following are their arguments in favour of this attitude.

Arguments against the Teaching of Venereal Prophylaxis to the Lay Public.—

- (a) The N.C.C.V.D. states that self-disinfection as adopted and carried out in certain sections of the army, where preventive packets containing the necessary antiseptics were distributed to the soldiers for their use, was found to be a failure, and that it did not materially reduce the incidence of venereal disease.
- (b) It believes that such propaganda and the facility of obtaining such packets from chemists would give the individual a false sense of security against venereal disease, and that in consequence the average individual would copulate promiscuously much more freely than before. The net result will be a failure, since the efficacy of the disinfectant in some cases will be counterbalanced by the great increase in the number of risks of infection.
- (c) It asserts that the average public is not sufficiently intelligent to carry out the prophylactic instructions in a proper manner, and that in many instances the procedure in the hands of the ordinary individual would fail to disinfect. Instances of such failure are given.
- (d) It maintains that the public would be inclined to use such disinfectant packets for treatment purposes, and that in consequence the patients would not come so soon to the clinics for proper and early treatment.

- (c) Finally, it believes that extensive disinfection propaganda and the great facility of obtaining the necessary packets would lead to an enormous increase in the amount of promiscuous intercourse between the sexes, and that in consequence the moral standard of the country would fall to a considerable degree.

The Arguments in favour of Venereal Prophylaxis Propaganda as brought forward by the Society for Prevention are the following :—

- (a) That venereal disease cannot be abolished either by preaching on its prevalence and dangers, or by early treatment of the cases as they arise, or by both measures together.
- (b) That a policy of prevention is better than a policy of early treatment and early cure.
- (c) That the arguments brought forward against the teaching of venereal prophylaxis to the lay public are untrue and unjustified.

The Author's Conclusions regarding the Correct Moral View. There can be little doubt that the controversy which has arisen is largely a religious or moral controversy. Those who argue against the general education of the populace on self-prophylaxis have a deep-seated conviction that it will lower the moral standing and decency of the general public, and religious bodies have been largely responsible in encouraging all arguments which tend to throw doubt on the efficacy of self-disinfection. One must feel a considerable amount of sympathy with the fears of the clergy and religious institutions, as well as with the views of the N.C.C.V.D. on this matter. The methods proposed by the Society for the Prevention of Venereal Diseases have been perhaps so bold and, one might say, sufficiently indelicate, as to perturb the higher feelings of certain individuals. In this matter, however, there is no middle course, and the author is in favour of educating the public thoroughly on the matter of prophylaxis against venereal disease. It may be some solace for the moralist to remember that cleanliness is next to godliness; and further, that throughout the ages the inhabitants of this earth have been more severely punished for ignorance and uncleanness than for wickedness and immorality.

Both are great crimes, but are we to believe that by refusing to bring into full daylight the crime of ignorance and uncleanness we shall diminish the crime of immorality?

The author has sufficient faith in the common sense and decency of the average individual in this country to believe that a thorough and full propaganda on these subjects would not lower the moral standard of the community.

The Author's Conclusions regarding the Correct Scientific View.—The opinion of the N.C.C.V.D. appears to be that gonorrhœa and venereal diseases in general can be successfully controlled and finally stamped out of our country by means of a propaganda of fear; and, moreover, their great hope appears to be early treatment. These methods, however, never succeeded with any known malady in the past. The only methods which have ever succeeded in respect of other communicable diseases have been true preventive measures.

Malarial fever has been stamped out of communities by prevention alone, and never by the isolation and treatment of early cases. Moreover, cases of malarial fever can be rendered non-infective by treatment much more easily than cases of gonorrhœa.

Typhoid, typhus, hydrophobia, smallpox, yellow fever, tetanus, plague, etc., have been successfully reduced to a minimum in civilised countries, by a combination of enlightenment and cleanliness on the part of the State and the populace itself. On the other hand, we can apparently bring forward no example of any disease which has been diminished by a campaign of partial education calculated to operate through the medium of fear, nor has the spread of any disease been successfully combated by early treatment even in combination with compulsory isolation.

So far we have had no striking success in reducing the prevalence of diseases such as measles, scarlet fever, phthisis, influenza and common colds, etc. The reason for this is that preventive measures are extremely difficult. The infection in these maladies is carried through the air and is breathed in and out of the respiratory passages. In most instances we do not know when the infective person is near, and, moreover, we can be infected from the dust of the streets. We must breathe, and in consequence we can give no formula of procedure which will give any certainty of safety to the individual whatsoever.

With venereal diseases and with gonorrhœa especially it is, however, very different. These are diseases which are contracted through actual contact of body surfaces. The infection does not live in the air or in the dust, and very rarely indeed is it conveyed by contact with inanimate objects. Gonorrhœa is practically always contracted by the contact of copulation. We have sufficient knowledge of the gonococcus to be able to formulate a procedure whereby the infection can be avoided almost to the point of absolute certainty. Is it not a crime, therefore, on the part of the State to withhold knowledge of this important nature from the adult individual?

The N.C.C.V.D. states that the knowledge has been given to the soldiers in certain sections of the army, and that, in spite of the free supply of the antiseptics necessary, it did not reduce the incidence of the disease. In reply to this, the author believes that the information given to these soldiers was superficial and inadequate, and that it was conveyed in many instances by medical men who had a very crude idea of the subject. Furthermore, that the amount of antiseptic ointment supplied was so insufficient as to be almost useless. The soldiers themselves were then blamed for the failure of a preventive procedure which would never succeed because of its lack of thoroughness. The N.C.C.V.D. states that the preaching of prophylaxis gives a false sense of security. This is untrue. It is the preaching of the safety of inadequate procedures which gives a false sense of security.

The success of preventive measures with regard to any disease has always depended upon their thoroughness. The measures recommended to safeguard against the contraction of venereal disease which have been advocated in the past have been very inadequate, and even those put forward by the Society for the Prevention of Venereal Diseases are in the author's opinion not yet sufficiently thorough to be certain. For example, it is usually recommended that the antiseptic ointments should be applied after copulation, whereas they should be applied both before and after.

The following is a procedure for men which the author believes is sufficiently thorough to guarantee a correct sense of security against gonorrhœa :—

- (1) Inject from a collapsible tube an inch of calomel cream into the urethra.
- (2) Smear the whole of the penis with this cream.
- (3) Pull over the anointed organ a sheath sufficiently large to reach the scrotum.
- (4) Smear the outside of the sheath with calomel cream.
- (5) After the act of copulation, remove the sheath and wash the hands and the penis thoroughly with soft soap.
- (6) Inject another inch of calomel cream into the urethra and smear the glans and the rest of the penis thoroughly with the cream.

The above is an absolute certainty against a gonorrhœal infection of the urethra, *provided the sheath does not break* in the act of copulation. If, however, the sheath breaks during the act it is not an absolute certainty. In the event of the sheath breaking, therefore, the anterior urethra should be injected with protargol, potassium permanganate or acriflavine several times, in the strength recommended in the abortive treatment of gonorrhœa (see next chapter). On no account, however, should it be preached that the procedure is safe where a sheath is not worn.

The prophylactic outfit necessary for the above measures must contain at least half a dozen sheaths of good quality,

One large collapsible tube containing $1\frac{1}{2}$ oz. of calomel cream.

" " " " $1\frac{1}{2}$ oz. of soft soap.

One collapsible tube containing 1 oz. of 2 per cent protargol jelly.

To the female the best advice that can be given is to see that the male possesses the necessary outfit and that he uses it in the proper manner.

She should also make free use of the calomel cream and free use of antiseptic douches, and she should be instructed as well in the measures recommended for her by the Society for the Prevention of Venereal Diseases. In addition to the above, careful instructions as to the cleanliness of the fingers, eyes, etc., should be given.

In the case of the prevention of syphilis it is necessary that further very special instructions should be given not only with regard to the lips, mouth and throat, but also with regard to the fingers, the skin of the scrotum, perineum, abdomen, etc.

It may be stated, perhaps with some truth, that the average individual would refuse to carry out a process so very objectionable as that just recommended above. It is none the less criminal to preach measures which, though less revolting, are still unsafe. The fault in the past has undoubtedly been the recommendation of methods which, though helpful, are still uncertain in their efficacy.

The safe procedure, objectionable as it is on account of its thoroughness, should certainly render the chances of contracting gonorrhœa 100,000 to 1 against. Do the moralists believe that the thorough teaching of this method to the adult population will increase the amount of promiscuous copulation a hundred times? Widespread information of this nature would be more likely to have the reverse effect. At any rate, as already stated, the author has sufficient faith in the public to believe that thorough knowledge will not cause a fall in the public morality even although safe procedures much less objectionable are devised by further researches against the diseases in question.

In the discussion of the prophylactic measures devised against gonorrhœa, it would be a serious omission not to mention here how great a blessing has been bestowed in this respect by the general introduction of Credé's methods against ophthalmia neonatorum. Whilst formerly the number of cases of gonorrhœal ophthalmia in maternity hospitals amounted to 10 to 14 per cent of the births, to-day, thanks to Credé's methods, this disease is now a rarity. Jos. Koch (1922) states that similar prophylactic instillations into the fossa navicularis after coitus, as recommended by Blokusewski, Frank, Neisser, v. Marschalko and others, against gonorrhœa in men, have been attended with much success. He further states that after the experiments of Blokusewski, Frank, and Welander there can be no doubt as to the success of this method. The only difficulty is to introduce the knowledge to the general public. Saudek (1921) suggests that an occlusive pessary worn by the woman, especially if medicated, might aid in warding off the transmission of infection from a gonococcal cervicitis to the male.

With regard to the institution of "ablution centres," there can be no doubt that they would be helpful in diminishing the amount of venereal disease contracted. Nevertheless, many victims of promiscuous copulation would be unable to make use of these centres, due either to the fact of excessive shyness or else because they had to hurry away to catch a train or omnibus in the late hours of the evening.

Finally, it would appear to the author that, viewed in the cold light of science, the case for individual prophylaxis against the serious menace of venereal disease is very strong. He believes, therefore, that much good would result if the two societies could agree to some plan of action on this matter whereby the necessary knowledge could be presented to the public in the least offensive and least harmful manner.

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CHAPTER XXXVII

INFECTION, INCUBATION, AND ABORTIVE TREATMENT OF GONORRHOEA

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COMPARATIVE CHANCES OF SUCCESS IN ABORTIVE TREATMENT OF GONORRHOEA AND SYPHILIS
—IMPLANTATION AND INITIAL LOCAL INVASION OF THE GONOCOCCUS—INCUBATION
PERIOD—VIRULENCE OF STRAIN—GENERAL RESISTANCE OF PATIENT—LOCAL RESIST-
ANCE—MALFORMATIONS—PHIMOSIS—PARAPHIMOSIS—THE MEATUS—HYPOSPADIAS—
THE IMPORTANCE OF EARLY DISINFECTION—ABORTIVE TREATMENT—VARIOUS METHODS
—URETHRAL INJECTIONS; SILVER NITRATE; ORGANIC SILVER SALTS—INJECTIONS
THROUGH CATHETER—SEALING UP OF MEATUS—IRRIGATION TREATMENT—INTRA-
URETHRAL DRESSINGS—INSTILLATIONS—ABORTIVE TREATMENT IN THE FEMALE—
CONCLUSIONS—THE WRITER'S METHOD—FUTURE PROGRESS.

NEXT to prophylaxis the abortive treatment of gonorrhœa is so important that the author has requested me to write this chapter on the subject.

Comparative chances of success in the Abortive Treatment of Gonorrhœa and Syphilis.
—In comparing, in their earliest stages, the two diseases gonorrhœa and syphilis as to the possibility of being able to nip the infection, so to speak, in the bud, we are presented with a very much more favourable chance of success in the case of gonorrhœa than in syphilis. The following are the reasons :—

A. *In Gonorrhœa.*

1. The sites upon which inoculation can take place are strictly limited and known surfaces of mucous membrane.
2. To such areas it is easy to apply antiseptics.
3. During the comparatively short incubation period, and even upon the appearance of the first clinical signs and symptoms upon which the diagnosis is established, the infection is still for all practical purposes a limited localised surface infection.
4. While yet a surface infection the gonococcus, being an extremely delicate organism, is easily accessible to local antiseptics and therefore easily destroyed.
5. In the newly-born, local infections occurring during birth are amenable to prophylactic measures or subsequent abortive treatment.

B *In Syphilis.*

1. Any accessible damaged area of skin or mucous membrane may provide a site of entry for the spirochæta.
2. The surfaces exposed during sexual intercourse through which infection is possible are therefore less limited in the case of syphilis, and so the application of local

antiseptics must perforce frequently be inaccurate. This inaccuracy will be more marked in the case of syphilis if the innocent infections occurring in the two diseases are included in this comparison.

3. The longer incubation period in syphilis enforces a greater delay in diagnosis and thereby in commencement of treatment.
4. During the incubation period there is a very striking contrast between the two diseases. As stated in the case of gonorrhœa the infection practically progresses as a surface spread, whereas in syphilis the spirochaetes rapidly seek the perivascular lymph spaces in the immediate neighbourhood of the site of entry. But a few hours will be sufficient to render all local attempts to sterilise such site—even if it be known—ineffective.
5. Even at the termination of the incubation period as recognised clinically by the appearance of the chancre, the most radical local treatment, *e.g.* wide excision of the chancre, will not abort the disease.
6. In syphilis we are faced with the established pre-natal intra-uterine infection which renders early or abortive treatment to the child impossible (excepting of course through the mother, in which directions great strides are being made and are already giving splendid results).

Happily intra-uterine infection does not occur in the child born of a gonorrhœal mother.

We have seen, then, in assessing by comparison the chances of success of early local treatment in the two main venereal diseases how very much greater are these chances in the case of gonorrhœa, which is by far the more prevalent of the two.

Before entering upon a historical and critical review of the abortive methods of treatment which have been evolved during the last two centuries up to the present time, it is necessary to study first in sequence the mode of entry of the gonococcus, its period of incubation, and the pathology of the disease in its very earliest stages. It is also necessary to discuss the various factors, local and general, which may influence the progress of the infection.

Implantation and Initial Local Invasion of the Gonococcus.—In the course of an attack of gonorrhœa—from its inception to its termination—the weakest link in the chain of the infection is the interval occurring between the date of the inoculation and that at which the first local clinical signs of the disease are discernible—commonly termed “the period of incubation.” By the “weakest link” one implies that it is in this period that the chain of infection is most easily broken, and moreover, with each hour that has been allowed to elapse since inoculation the harder becomes the chain to sever.

The factor which controls the success or otherwise in any rational medical procedure devised with the object of bringing about the complete early eradication of the as yet local gonococcal infection is *the accessibility of the gonococcus*. In proportion as the interval of time lengthens after the implantation of the infecting gonococcal medium upon the exposed surfaces of the genital mucous membrane, so correspondingly does the invading army of gonococci become larger by rapid and progressive multiplication, and also more resistant. In the *male* the infection progresses by direct extension beyond the fossa navicularis to involve the adjacent mucous membrane of the penile urethra—studded with its numerous crypts and glandular orifices which provide most convenient strongholds for the multiplying gonococci. In the *female* the extension of the infection is by no means localised to the urethra; in fact, the cervical canal is frequently simultaneously, if not the first to be, attacked; and in addition it is obvious that the same applies with regard to the para-meatal follicles, and also to the orifices of Bartholin's ducts in that they are all liable to contamination with gonococcal material during the act of coitus at which infection was transmitted.

During the **incubation period**¹ which in the great majority of cases will be limited in extent to between forty-eight and one hundred and twenty hours—it may be assumed for practical purposes, at any rate in the male, that the gonococci advance by direct surface extension.

Not only is there this progressive direct spread along the epithelial surfaces mentioned, but also an accompanying lowering of resistance of the epithelial cells involved by the damaging effect of the gonococcal toxin. In fact, the toxin is continually exerting this damaging influence at the periphery, and so rendering more easy the advance of the multiplying gonococci by which it is formed.

With the appearance of the first clinical signs of the established disease the local extension of the infection becomes much more rapid—not only as a surface spread, but by penetration beneath the damaged and cast-off superficial epithelial cells. It also invades the orifices of the numerous minute gland-ducts opening upon the surfaces involved.

The extension will vary in rapidity and degree as the balance swings between the virulence of the individual strain of gonococcus on the one hand and the local and general resistance of the patient on the other.

Virulence of the Strain.—Most clinicians have experienced instances where two or more patients have been infected from a common source in whom an abnormally short incubation period of say twenty-four hours or even less has been followed by rapidly developing and severe local and general disturbances as the attack of gonorrhœa progresses.

There are on record isolated cases terminating fatally in a gonorrhœal septicæmia within a few days of infection.

However, with regard to the fatal cases of septicæmia, in the great majority of those published it has developed somewhat late in the infection following gross involvement of the adnexa, viz. the epididymis, prostate or vesicles in the male and the uterus and Fallopian tubes in the female. This would point, therefore, to a low resistance on the part of the patient rather than to an exceptionally virulent strain of the gonococcus.

On the other hand, the writer has personal experience of an instance where two medical students were exposed to a common source of infection throughout the same night. Neither took any precautions, nor had either of them suffered previously from gonorrhœa. The one escaped infection, and the other developed gonorrhœa on the morning of the fifteenth day, following a drinking bout the previous evening. There had been no intercurrent risk.

Bacteriologists and clinicians long since have recognised that vaccines prepared from certain cases give better results than others. Sometimes by pure chance when the same reliable technique is being employed in a laboratory as routine, a particularly good immunising strain of gonococci is happened upon which will provide a vaccine possessing a powerful antigenic property. This can only be explained by the variation in "strain"; although of course it does not necessarily follow that a strain which clinically suggests high virulency will therefore furnish a vaccine of extraordinary therapeutic power when grown *in vitro* on artificial media.

General Resistance of the Patient.—This would appear to play a less important part during the earliest stages of an attack, whilst the infection is as yet local, than during the later phases of the disease. Numerous instances are recorded in which the gonococcus has been grown from the blood during the subacute and chronic stages of uncomplicated

¹ Some observers, however, go so far as to state that in little more than 50 per cent of cases would the incubation period come within the limit of from three to five days as commonly asserted.

Asch states that in his experience from three to four weeks frequently may elapse before the appearance of the discharge, and in fact an incubation period of four to eight weeks is by no means uncommon.

Instances of a very long incubation period are recorded in cases where infection occurred during intercourse at or about the menstrual period with a female who is the subject of an old latent infection. The attenuated gonococci are more prone to come to the surface under such conditions.

cases. In the great majority of chronic cases the gonococcus probably circulates in the blood. It is in the prevention of the development of this septicæmic state that the general resistance must play the most important rôle.

There is little that can be stated with any degree of accuracy as to the conditions which go to increase or diminish the general resistance of a subject about to become infected with the gonococcus as apart from other infections.

We do know definitely that one attack does not confer an immunity against subsequent infections; on the contrary, many agree that the incubation period is generally shortened in such, unless some years have elapsed since an absolute cure.

Some of the older writers have described types such as the blonde and the sallow toxic subject in whom the infection rapidly becomes very acute, and subsequently resistant to treatment.

Some will aver that an infection contracted by a European from a native in a tropical country is usually very rapid and severe in development. Toxæmias and wasting diseases which tend to lower the general resistance against any or an additional microbic invasion will play a more important part, as stated above, during the later rather than the earlier stages of the infection.

The Local Resistance.—This is probably the most important factor influencing the initial onset of the disease, as evidenced by the length of the incubation period and the severity of the local subjective symptoms.

The epithelium of a urethra which is maintained in a chronic state of congestion by the local irritation resulting from a life of sexual and alcoholic excesses provides a fertile soil for the gonococcus.

The too frequent usage of irritating antiseptics after exposure to infection, either as injections in the male or douches in the female, is also prone to set up a state of chronic congestion, if not inflammation, of the genital mucous membranes.

How often does one listen to the lament of the patient that had the trusty syringe or douche been available the infection would not have occurred. Infections which do occur under these conditions are generally characterised by the rapidity of onset and extension.

A patient suffering from a non-venereal urethritis—either bacteriological, chemical, or mechanical (such as that accompanying a stricture), or a combination of any of these—possesses a low resistance to the gonococcus locally. Similarly a woman suffering from leucorrhœa with chronic cervicitis, or mechanical and microbial vaginitis accompanying the wearing of a pessary, is handicapped to withstand the onslaught of the gonococcus. Should the first symptoms develop with the commencement of a menstrual period, extension is rapid and local treatment difficult. It often happens in the case of the prostitute that frequent repetitions of the sexual act are only discontinued when rendered too painful by the local inflammation. In such instances, where, instead of the infected genital mucous membranes remaining more or less in a state of rest during the incubation period, they are subjected to such intense vascular and mechanical disturbances as must necessarily accompany the act of coitus, the onset of the disease is usually marked by very severe local disturbances in both sexes. Certain vigorous exercises such as cycling, running, dancing, etc., are similarly lowering to the local resistance during the incubation period.

In the virgin infected with gonorrhœa at the first coitus, the attack is frequently very acute. This might be explained by the local lowering of resistance should the bruising and laceration of the genitalia have been severe.

The local resistance of the mucous membrane in the virgin to pathological microbial invasion is probably lower than that of the woman who regularly indulges in sexual intercourse.

A factor which must play an important part in the local resistance of the urethral mucous membrane to gonococci is the reaction of the urine at the time of infection and during the incubation period.

It frequently must happen that the transmission of infection occurs at a time when the urine of both parties is markedly acid, to which the gonococcus is very tolerant as compared to its high susceptibility to but weakly alkaline solutions.

It is probable, therefore, that a person passing alkaline urine during say the twelve hours following exposure to infection has a better chance of escaping gonorrhœa than when passing acid urine, especially in the male.

We know that gonococci will not grow on a culture medium, otherwise favourable, if the reaction be made but faintly alkaline; similarly, if a medium in which gonococci are growing abundantly be rendered faintly alkaline the culture is destroyed (See Chap. VIII.).

The reaction of the urine, therefore, must be an important factor in determining the duration of the incubation period by influencing the rapidity of growth and extension of the gonococci.

Most clinicians endeavour to ensure by medication that the urine shall be maintained alkaline both during and subsequent to the administration of abortive treatment.

Malformations.—**Phimosis**, if marked, is always accompanied by some degree of balano-posthitis from retained smegma, and is a severe handicap to a patient exposed to infection. A patient with phimosis is, moreover, more liable to contract the disease on exposure, since self-disinfection is more difficult to accomplish, and also because gonococci can reside and multiply for a considerable period within the preputial sac and subsequently infect the urethra, which otherwise might possibly have escaped. Unfortunately, when infection has occurred under such conditions, abortive measures of treatment are thereby rendered impracticable in the majority of cases. Should a condition of **paraphimosis** complicate the sexual act at which infection occurred, and same is not relieved by reduction, the incubation period is shortened, and in addition there is a marked exacerbation of the local swelling and cedema with the appearance of the discharge. The infection rapidly extends along the urethra behind the constricting band. The pressure applied to the parts during the manipulation for reduction is also not calculated to increase the resistance of the urethral mucous membrane.

In an obstinate case, therefore, a dorsal incision is always preferable to prolonged attempts at reduction by manipulation.

Nature's attempt at Bier's treatment thus accidentally applied to the fossa navicularis meets with ill success during the incubation period of gonorrhœa.

Concerning the Meatus.—In the writer's experience the size and shape of the meatus in the male appears to exert some influence on the likelihood of a patient escaping infection or otherwise. The meatus is smaller in those who have been circumcised when but a few weeks old, at which date the penis is in a miniature stage of development. In his opinion the development of the meatus subsequent to birth is governed by the "tug" of the frenum which is exerted upon the posterior fissure of the meatus during erection, and as the glans enlarges with age the frenum tends to fix this point. The absence of this controlling frenal drag upon the posterior angle of the meatus would explain the relatively high incidence of the small meatus amongst the Jews. In the presence of a short and tense frenum it will be seen when the penis is held in the horizontal position that the meatus is directed downwards and forwards, whereas in the circumcised it is directed forwards and upwards.

With the very redundant or phimosed prepuce the frenum is usually lax, and complete retraction is impossible. The frenum, therefore, is not under tension during erection. This would explain the small meatus which generally accompanies this condition, which at first sight would appear to be a contradiction to what has just been said.

On purely mechanical grounds, one would expect that infection would be more certain to occur through a large patulous meatus than through a small and compact one. In the case of the latter, both the meatus and the adjacent fossa navicularis are of a certainty subjected to a more forceful and efficacious scouring during the first act of micturition following exposure than in the case of the large meatus.

Hypospadias.—Though hardly coming within the scope of this chapter, one might make a few remarks with regard to the effect this condition in its milder forms has upon the earliest stages of gonorrhœa. Either the first degree of hypospadias is a much commoner condition than is generally supposed, or else the incidence of gonorrhœa amongst such subjects is very high, if one judges from the number of patients under this category one sees amongst gonorrhœal cases. The writer believes that they are more susceptible to infection, and that the absence of the fossa navicularis with its protective lining of pavement epithelium, upon which the gonococcus does not grow rapidly, is the explanation.

In the commonest form—hypospadias of the glans—the frenum is absent and the urethra terminates anteriorly in a small orifice at the base of the glans. The upper wall only of the urethra is continued forwards, and represents the exposed roof of the fossa navicularis. Frequently a shallow meatus persists as a *cul-de-sac*. Whether or not we accept the theory that the normal fossa navicularis functions in some small degree as a protective structure, yet the writer is confident that most clinicians will agree that in these cases in which the fossa is absent the incubation period is very short; and moreover, the gonococcal infection becomes mixed by the addition of secondary organisms at a much earlier date than usually occurs in the presence of a normal fossa.

With regard to the much rarer penile or second degree of hypospadias, with the exception of the most advanced type in which the urinary orifice is situated at the peno-scrotal junction, no unsurmountable difficulties are presented to the carrying out of abortive treatment should such a subject contract gonorrhœa.

In both types (first and second degree) the urinary orifice is frequently very small indeed, and is accordingly easy to close with a sealed dressing as described later under the technique of abortive treatments.

Should such attempts at an early cure be unsuccessful, or should the patient fail to present himself for advice until the disease is deep-seated, these cases are very intractable to treatment, and there is always present a heavy infection of superadded secondary organisms.

Penile hypospadias is sufficiently rare to make it questionable whether mention should have been made of it, and malformations of greater rarity are beyond the scope of this book.

The Importance of Early Disinfection.—If a patient has exposed himself to the risk of contracting gonorrhœa, and if we assume that he has become contaminated, then there are three chances of aborting the complaint. These chances or opportunities may be arranged in the following order of merit, according to the periods of time which have elapsed since such contamination :—

1. Immediately after exposure.
2. During the period of incubation.
3. On the very first appearance of signs or symptoms of the established disease.

Nos. 1 and 2 come under the category of immediate and delayed prophylactic treatment, of which every person should be encouraged to avail himself after exposure.

By increasing (*a*) the knowledge of the community on this subject, and (*b*) the number of clinics at which such opportunities for treatment are available at all hours, we shall be making a sound and practicable effort as a nation towards lowering the incidence of gonorrhœal infections.

The chances of completely eradicating the infection by the immediate and thorough application of suitable gonococcicides should be 100 per cent, but in the absence of such measures the percentage falls with every hour which is allowed to elapse after exposure.

The reasons for this are obvious, since the earlier treatment is commenced—

- 1 The smaller and less resistant is the invading army of gonococci.

2. The greater the chances of reaching and therefore destroying every individual gonococcus.
3. The more tolerant will the mucous membrane be to the local antiseptics.

The writer is unable to find mention of any accurate research—if such ever has been made—with regard to the rate at which the gonococci progress along the urethral surface during, say, the first twenty-four hours following infection. Since such investigations necessarily would have to be carried out upon the human urethra in order to furnish reliable clinical data, obviously they would be confronted with many obstacles. From the clinician's point of view we have already shown that there would appear to be many factors influencing the rate of spread as indicated by the variable duration of the incubation period. It would, however, be very valuable to possess some accurate knowledge as to the average progress made by the infection in, say, the first six hours, in deciding how far we are justified in guaranteeing to the community the absolute efficacy of self-disinfection by the various methods at present advocated. By all means let us encourage the routine employment of immediate self-disinfection both *before and after* exposure to infection, since not only are we dealing with the possibility of gonorrhœa, but also the simultaneous inoculation of syphilis and chancroid. What the writer would emphasise is the danger of too much reliance being placed upon the patient's own attempts at disinfection, which frequently must be performed under difficulties sufficient to render them anything but thorough, even if he be intelligent and sober. Those in charge of venereal clinics know only too well how frequently such "precautions" taken by the patient have given a false sense of security. In some instances the patient even delays reporting the earliest manifestations of the disease, imagining that the local disturbance has been produced by an over-vigorous application of the particular "outfit." It should be impressed upon the community, therefore, that not only is immediate self-disinfection absolutely essential, but that in addition, after a minimum of delay, this should be supplemented by the most thorough methods deemed necessary by a competent medical man, or at a public clinic. Moreover, attendance should continue at such until pronounced unnecessary.

Were the above procedure carried out universally, treatment could be commenced at the very first signs of the established infection in practically every instance in which the prophylactic measures failed.

The Importance of Early Disinfection as proved by Statistics.—During the war the American army collected valuable statistics as to the importance of immediate disinfection after exposure to venereal diseases.

Colonel Walker, U.S.M.C., gives the following facts:—

In one group of 3600 men in which the exposures were estimated at 100 per cent the venereal rate of infections worked out at 720 per 1000 per annum.

After the introduction of compulsory disinfection, which meant that every man who returned from pass was disinfected whether he admitted exposure or not, the infections dropped to 10 per 1000 per annum.

In another group, 1246 admitted exposures were disinfected within one and a quarter hours, with the result that only two infections developed.

The routine method of disinfection employed was as follows:—

1. Thorough washing with soap and water.
2. Washing with a solution of perchloride of mercury.
3. Urethral injection of 2 per cent protargol or 10 per cent argyrol, which is retained for three minutes.
4. Inunction of parts with 30 per cent calomel ointment.
5. Wrapping the penis in toilet paper for four hours.

The above two instances speak well for early disinfection when carried out *under supervision*.

Lieut.-Col. Young, U.S.M.C., emphasises the importance of early disinfection, giving as an illustration the facts that in one battalion in France to which all-night passes were frequently issued the incidence of venereal disease was three times that of an adjoining battalion in which the men had to return the same night. There was considerably less delay in disinfection after exposure in the latter.

Rigg's table, now become classical, illustrates the relative value of disinfection applied at various periods after exposure to venereal infection as carried out at the naval station, Norfolk, Virginia, during the years 1915 to 1917.

Out of a total of 5103 men who had been exposed to infection, 1180 were disinfected within the hour, with the result that only one developed a doubtful lesion which healed in two days. As the interval after exposure increased, so the percentages of infection rose markedly after four hours, and if applied after an interval of ten hours had elapsed the incidence of infection appears to have been uninfluenced by such measures.

One must always take into consideration the fact that there are two main sources of error which tend to render the collection of absolutely accurate figures impossible when dealing with venereal exposures and infections:—

1. The honest belief and hope of the over-keen clinician and his staff that the methods under investigation are producing good results.
2. The hypocrisy of a community subjected to such investigation.

With the following remarks we will conclude the discussion as to the means of aborting the infection prior to the first appearance of the clinical signs of the established disease.

Immediate self-disinfection is to be strongly recommended and encouraged, since it frequently happens that a person is so circumstanced that for several days he is unable to procure the more thorough disinfection under medical supervision.

In the selection of the constituents of the "outfit" advocated for the carrying out of self-disinfection due consideration should be taken as to practicability and efficacy.

Such an "outfit" should be easily procurable, compact, cheap and non-irritating. To ensure that the immediate application is rendered possible an outfit should be carried always by those in the habit of exposing themselves frequently to infection, in addition to a safe rubber sheath. The tremendous importance of immediate self-disinfection, and the essential details in carrying out the same, should be explained to every young male as part of his instruction on sexual matters. Such extraordinary and necessary precautions should tend to impress upon him the prevalence, infectiousness, and gravity of these dreaded diseases to which promiscuous sexual intercourse would inevitably expose him.

Finally, it should be impressed also upon the community that protection against venereal diseases as provided by the above precautions is not absolute, but in the case of gonorrhoea very nearly so. The fallacies, therefore, should be pointed out as a guard against too great a reliance being placed upon them.

Whether the patient has been able to carry out immediate self-disinfection or not after exposure, he should make every effort to obtain as soon as possible the most essential and thorough local treatment under medical supervision. He should also remain under medical surveillance until discharged.

Supervised Early Disinfection.—When such a patient presents himself for advice after exposure the following facts should be carefully elicited by the medical adviser: What immediate or delayed precautions already have been taken by the patient? Under what circumstances did the exposure take place? Was he sober at the time? Had he suffered from any pre-existing urethral infection—recent or remote? Is he married or single? What are the dates of the previous three exposures?

Whether or not in the opinion of the medical man the patient has already carried out immediate self-disinfection with a thoroughness likely to be effective, the writer would suggest the following procedure:—

- (a) Note the amount of local irritation he may have produced already.
- (b) Gently obtain a specimen from the fossa navicularis with a platinum loop, and immediately examine same after staining by Gram's method.
- (c) If micro-organisms are detected, proceed to exclude pre-existing infection, which should not be difficult at this stage. In the absence of other clinical evidence a pure infection with gonococci would point strongly to recent implantation.
- (d) Examine the urine by the two-glass test.
- (e) If pre-existing infection should be proved, the case will not come under the category of those suitable for abortive treatment (consider the dates of previous exposures).
- (f) Should these investigations fail to detect any evidence that infection has occurred, then proceed as follows :—
- (g) After he has urinated as above, thoroughly disinfect the meatus, glans, preputial sac, and especially the orifices of Tyson's ducts in the frenal angles.
- (h) Administer a thorough urethro-vesical irrigation of potassium permanganate 1 in 2000, as warm as can be comfortably tolerated, followed on the same evening (six to nine hours later) by another of 1 in 3000. On the following two days repeat the irrigation morning and evening, being guided as to the strength of the solution by the local reaction. A thorough inunction of the parts with 30 per cent calomel cream should be carried out at the close of the first attendance only. The patient should be ordered to wear a suspensory bandage during this period, and to refrain from vigorous exercise or work if possible. There will be a minimum of local reaction if he remains at rest with the penis maintained in the upright position along the abdomen. He should be instructed to drink copiously to ensure two-hourly urination, and to take an ounce of the following mixture after each meal—four doses in the day :—

R. Sodii bicarb.	grs. xxx.
Pot. citrat.	grs. xv.
Helmitol	grs. x.
Tr. hyoscyami	℥ xx.
Aq. cinnamomi ad	5 i.

The writer has yet to meet with a case in which gonorrhœa has developed after the above procedure where treatment was commenced within twenty-four hours of exposure—even though the initial self-disinfection in many instances has been anything but thorough, and in several cases entirely neglected.

This only refers to cases in which no infection could be detected on the first attendance, and of course it is impossible to say in how many it was ever present.

In dealing with those patients who first attend in the interval 24-72 hours after exposure, the writer advocates that even in the absence of clinical signs they should be treated along the same lines as those in whom the infection actually can be proved, that is to say, by one of the methods recommended in the abortive treatment of the established infection, which will be discussed presently.

Less vigorous measures hold out but poor chance of success when commenced after an interval exceeding twenty-four hours has elapsed since exposure, should the gonococcus have become implanted in the urethra during such exposure.

The Abortive Treatment of Gonorrhœa (proper).—This term as generally applied to gonorrhœa refers to the various procedures which have been devised with the object of eradicating the infection upon the first appearance of the earliest clinical signs of the established disease.

Strictly speaking, therefore, it is inaccurate to use the term "abortive," in that the disease is already manifest.

The preceding paragraphs have dealt with abortive treatment applied only under the

assumption that the infection *may be present*. In this sense the treatment is only actually abortive in those cases in which the mucous membrane has really been inoculated with gonococci. In the following discussion of the various procedures advocated with the object of cutting short an attack of established gonorrhœa in its earliest stages, the writer would have preferred to substitute the term "early intensive treatment" in place of "abortive treatment." However, the latter term appears to be so universally adopted throughout the literature, that it has been decided to adhere to it in this chapter in order to avoid confusion.

An attack of gonorrhœa frequently can be diagnosed a few hours prior to the appearance of the discharge, should a patient who is apprehensive be kept under regular observation from the time of exposure. On careful questioning, one is told by the patient that there is a slight intermittent itching in the urethra in the region of the fossa navicularis. Subconsciously his attention is directed towards his penis, which he is constantly handling. Should the patient have had a previous attack, then frequent squeezing and milking the urethra in his anxiety to detect a discharge might easily mask the above premonitory symptoms. If it is the first attack he will be less critical, and such early symptoms will in all probability pass unnoticed. Again, if he has received immediate or delayed prophylactic treatment, there will be present in varying amount some chemical urethritis which might be misleading to the unexperienced. With any of these possibilities often some hours of the most valuable time may be saved by the examination of specimens obtained by gently stroking the walls of the fossa navicularis with a platinum loop. One still hears of cases being told to return to a clinic the next day "if a discharge appears, or gets worse," when an immediate examination might have settled the diagnosis. How much better it would have been to have commenced abortive treatment at once.

In the untreated case there is now a rapid increase in the *symptoms*. What was a suspicion becomes a reality. The slight itching becomes a dull, throbbing, burning sensation, which is increased immediately after micturition. The first noticeable *signs* now appear. If the patient be circumcised, or the glans is habitually exposed, the meatus becomes sealed up with the dried surface portion of a scanty, thin, glairy, sero-purulent discharge. If, however, the glans is constantly moist beneath a redundant prepuce, the meatus will not become temporarily sealed with the discharge. The lips of the meatus will become slightly swollen and discoloured, and the orifice thereby narrowed. Sometimes the edges may be pouting and somewhat everted.

On separating the lips of the meatus the exposed walls of the fossa will appear red and congested, with several minute milky patches on their surfaces.

Stained specimens of the discharge at this date will show numerous gonococci chiefly lying free, and several will be seen adhering to the surface of the large squamous epithelial cells cast off from the fossa navicularis.

Similarly there may be a few cylindrical epithelial cells from the adjacent portion of the urethral mucous membrane. At this stage pus cells will be scanty, but a few well-defined polymorphonuclear leucocytes will be seen containing gonococci within their protoplasm. Subsequently, in the untreated case, as the discharge becomes more purulent the intracellular arrangement of the gonococci within the abundant leucocytes is a striking feature.¹ Many of the cells lose their definition as degeneration ensues.

From the point of view of prognosis, some observers lay considerable stress upon the significance of the very early appearance of abundant pus cells crammed with gonococci.

They argue that this evidence of early and energetic phagocytosis is direct proof of the natural resistance of the infected individual to the gonococcus; and further, that those cases which are characterised by this early reaction invariably do better clinically

¹ Panton emphasises the diagnostic importance of the characteristic intracellular grouping of the gonococci, which are arranged in pairs, evenly distributed throughout the cytoplasm of the pus cell, and not grouped together into one area. Intracellular staphylococci, for instance, are usually clumped together in an irregular manner in one portion of the leucocyte.

than those in which it is delayed. Finger is stated to have failed to infect with gonococci patients suffering from fever with general marked leucocytosis. Several instances are recorded of rapid spontaneous cure under a co-existing hyperpyrexia, such as in malaria, etc. The more generally accepted explanation is that the high temperature is probably a more potent factor than the leucocytosis. In the writer's experience, should a high temperature, from whatever cause, develop during the course of an attack of gonorrhœa, such improvement as may occur is only temporary and follows the temperature chart significantly.

Why does the urethral discharge practically cease during the acute phase of an attack of epididymitis? Is this due to the accompanying rise in temperature, or to the leucocytosis? One would imagine the former is responsible, since the latter should temporarily increase the discharge.

Many ingenious devices have been introduced into the local and general therapy of gonorrhœa with the object of producing an increase in temperature and in phagocytosis.

To return to the significance of the presence of intracellular gonococci, as to what bearing this phenomenon may have upon the success or otherwise in the early or abortive treatment of gonorrhœa, one can say definitely that it is preferable to commence such treatment when the evidence that phagocytosis has commenced is at a minimum. The reason for this is entirely a matter of how far the infection has progressed. That is to say, the presence of polymorphonuclear leucocytes containing gonococci is proof that the infection has penetrated down between the interstices of the urethral columnar epithelium to be encountered by the wandering phagocytes which have left the capillaries with this object. The gonococci do not penetrate the stratified squamous epithelium of the fossa navicularis. In the initial attack of gonorrhœa the infection progresses more rapidly than in subsequent attacks, provided that the urethral mucous membrane has had time to recover from all inflammatory processes. This is generally explained by the statement that the normal cylindrical epithelium of the urethra suffers considerable damage from the gonococcus; so much so, that large areas are destroyed. In the subsequent processes of repair this is never replaced by cylindrical but by pavement epithelium, which is more resistant to the gonococcus. One would expect, therefore, that the early intensive or abortive treatment should give better results in second or subsequent attacks of gonorrhœa than in primary infections, since in the former the urethral mucous membrane will be less vulnerable and less easily penetrated by the gonococcus, and also more tolerant to local treatment.

This seems to be the universal opinion of most clinicians who have had considerable experience with the abortive treatment of gonorrhœa. Some even go so far as to state that they are able to abort every attack of gonorrhœa if taken within the first twenty-four hours, with the exception of primary infections.

When one reads the descriptions of some of the earlier methods used in the "abortive treatment" of gonorrhœa, one feels that the damage produced by such drastic measures must have exceeded by far that which might be expected to result had the case gone untreated.

Experience having taught that urethroscopic examination is indispensable to accurate diagnosis in every case of chronic urethritis, such routine examinations form part of the daily work of every modern specialist dealing with such cases. The wider one's experience becomes from these examinations, the more one realises that the injudicious application of chemicals within the urethra is responsible for as much damage as, and frequently more than, the gonococcus itself. In full recognition, then, that the "abortive treatment" is by no means devoid of risk, it behoves every clinician to undertake such procedure with extreme caution. It is of the utmost importance that one should avoid the production of such severe local reaction that from this cause alone treatment has to be suspended. The intensive treatment should be such that in the event of its proving unsuccessful by the end of a week at the outside, then the patient can continue without

interruption under one of the schemes of routine treatment as advocated in Part VI. By far the most important factor towards success—given a rational method of intensive treatment—is the proximity of its application to the commencement of the initial symptoms. In very few instances is it justifiable to attempt such treatment if more than forty-eight hours have elapsed. Early within the first twenty-four hours is the ideal, therefore it is but very rarely that it can be undertaken amongst out-patients, who seem always to wait until the discharge is thick and purulent on the third or fourth day before attending. Not until the general public has thoroughly grasped the fact that only by reporting at the earliest date is there an excellent chance of curing the disease in a week by means of intensive treatment, shall we see an increase in the number of cases in which this treatment is applicable.

The percentage of early cures obtained by the various workers with modern abortive methods varies somewhat widely. The extremes would appear to be furnished by Frank and Lewin of Berlin with a claim of only 45 per cent of successes on the one hand, and by Ballenger of Atlanta with his 90 per cent on the other. Recent statistics from different sources show on an average from 60 per cent to 70 per cent of cures in cases where treatment was begun in the first forty-eight hours after the commencement of the symptoms. The figure is higher if only those cases treated within the first twenty-four hours are analysed.

From this it would seem reasonable to state that there is a very excellent chance of curing within a week every two out of three patients suffering from gonorrhœa, if they can only be induced to report within twenty-four hours of the appearance of the very first symptoms.

Some of the methods which are advocated make a considerable call upon the time at the disposal both of the surgeon and the patient, so much so that they are hardly practicable in the case of the "out-patient." Other methods, apart from the frequent interruptions necessitated in the patient's employment, also render any occupation other than that of a sedentary type out of the question. However, the above difficulties can generally be overcome by a judicious combination of medically supervised hospital treatments supplemented by intervening self-administered injections on the part of the patient. Many cases have been successfully "aborted" in this manner. There can be no doubt that complete rest in bed holds out the best chance of success, and every clinic should be equipped with beds for this purpose. There will be a lessened incidence of local complications, and, moreover, under these conditions the patient is maintained under suitable dietary, regular medication and constant observation.

The various methods for the abortive treatment of gonorrhœa which have been devised fall under one or more of the following procedures :—

1. *Urethral Injections.*

- (a) By means of a syringe applied to the meatus.
- (b) By means of a soft catheter passed as far as the bulb.
- (c) The gonococcicide introduced as in (a) is retained by sealing up the meatus for varying periods.

2. *Irrigations.*

- (a) Anterior, down to the compressor muscle.
- (b) Urethro-vesical, by applying nozzle to meatus.
- (c) Urethro-vesical, by first filling the bladder through a soft catheter, followed by a natural evacuation.

3. *Intra-urethral Dressings.*

4. *Instillations.*

- (a) The gonococcicide is applied to the urethra on a pledget of cotton-wool passed on a suitable introducer through the meatus down to the bulb and then withdrawn.

- (b) As above, excepting that the instillation is made through the cannula of an anterior urethroscope under direct observation.
 (c) Instillation by means of medicated bougies.

5. *Electrolytic Treatment.*

Urethral Injections.—The somewhat drastic measures adopted by the pioneers of over two centuries ago in their endeavours to eradicate the infection by means of the introduction of strong solutions of silver nitrate, etc., into the urethra have very slowly undergone modification up to the present date.

Among such pioneers and their successors who attempted to abort gonorrhœa mainly by the employment of caustic agents, should be mentioned Musitanus (1701), Fordyce (1758), Warren (1771), with others, during the eighteenth century, and later towards the middle of the nineteenth century we come to Ricord and Debeney, prominent amongst the French school. Of more recent date we have Feleky (1894), who attempted to abort the infection by swabbing out the urethra with 5 per cent silver nitrate from a point below the seat of the infection. Welander (1892) injected 2 per cent silver nitrate solution to be retained in the urethra for two minutes, after having thoroughly cleansed the canal with swabs. He claimed that one such application would cure the disease in two to three day old cases.

Pontoppidan used instillations of silver nitrate into the fossa navicularis. Amongst the experimenters who employed various agents for this object we have Lloyd (1850), who tried zinc chloride 1 in 480; Venot (1850) used chloroform 1 in 30; Kuechenmeister (1880) used aqua calcis and alum; Ullman (1897) used sublimate; Neisser (1889) silver nitrate 1 in 3000 to 1 in 1000; Janet and also Reverdin (1892) each advocated potassium permanganate 1 in 2000 to 1 in 1000; and Koester (1890) with Jadassohn (1892) favoured ammonium sulpho-ichthyolate 1 per cent to 5 per cent. For the above historical facts the writer is indebted to Bierhoff's paper entitled "Further Notes on the Abortive Treatment of Gonorrhœa in the Male," read before the New York Physicians' Association, January 24, 1918.

Lyons (1905) advocated the following method:—The patient passes water, and the surgeon injects $1\frac{1}{2}$ dr. of a 4 per cent solution of nitrate of silver into the urethra with an ordinary syringe; the meatus is then held so as to retain the solution for two or three minutes. The gonococci may disappear in twenty-four hours, and if so nothing further is done. If gonococci are still present $1\frac{1}{2}$ dr. of a 2 per cent solution of silver nitrate is injected, and the patient re-examined in twenty-four hours. If the gonococci have not disappeared, a third injection of a 1 per cent solution may be used; but if this fails to cause disappearance of the gonococci, it is useless to proceed further with the method, and the "symptomatic plan" is adopted. By this means the author claims to have cured the disease in six days in 95 per cent of over 400 cases.

It is really surprising, in face of the prevalence of gonorrhœa, that progress in this direction has been so slow. Doubtless the distress occasioned to the patient, and the generally unsatisfactory results obtained—immediate and remote—did not tend either to enhance the popularity of these early attempts or to stimulate further investigation. Wyeth in an article on the subject quotes from the 1912 edition of Keyes the following two sentences: "In the production of chronic urethritis the abortive treatment has taken the place of the sound of our fathers"; and again: "The surest way to abort gonorrhœa is not to try to abort it." Wyeth criticises the above statements as being very unfortunate teaching. Bierhoff also illustrates the attitude of opposition adopted by certain of the American authors. Thus he quotes the following statement of Guiteras: "The abortive treatment of gonorrhœa is now rarely used by men doing special work in urethral diseases," and mentions that Chetwood "does not favour its employment, yet seems not to speak from personal experience with the method." Bierhoff, with Wyeth, also alludes to the aphorisms of Keyes, but adds that he would paraphrase his (Keyes) statement by saying

that "the surest way to abort a gonorrhœa is to know when to attempt it and how to do it." From a purely historical point of view, to the writer's mind, these remarks furnish a good illustration of the disrepute into which the attempts at abortive treatment have fallen from time to time, and on this occasion but eleven years ago. However, present-day workers owe much of their knowledge to the experience gained from the too energetic methods of these early enthusiasts. It therefore behoves us not to bring abortive treatment again into disrepute by over-confidence.

Silver nitrate is being used less and less in the abortive treatment of gonorrhœa, on account of the destruction of the epithelial cells resulting from the coagulation of their albumin. The effect of its introduction into the urethra, in the concentrations advocated in the past, is comparable to giving the same a coat of paint beneath which the deeper gonococci are lying unaffected in the intercellular spaces. To administer AgNO_3 in sufficient strength and quantity with the hope of reaching these, means the destruction of the mucous membrane to a similar depth. Certainly it destroys gonococci in weak solutions provided it can reach them; but in the writer's experience, even when so used, it is very prone to set up a "chemical gleet," which on the invasion of secondary organisms may develop into an intractable urethritis. He would never use it in any acute or subacute urethral conditions. The certain discharge resulting from its local application frequently is induced in order to provide specimens for a "test of cure."

With the advent of the **organic silver preparations** at the beginning of the twentieth century the abortive treatment became more popular, and various methods arose embodying their employment. They were proved to be effective gonococcicides, and extremely well tolerated by the urethral mucous membrane. Experimentally they were found to possess a reasonable power of penetration (Benario, Schaffer, Pezzoli, and Kamer). The features common to the majority of these preparations—and they have now become numerous—are that they are albuminates, are non-destructive to epithelium in moderate strengths, and decompose on prolonged exposure to light. Their solutions should be freshly prepared by dusting the powder on cold distilled water. They are not affected by soluble chlorides, and do not precipitate albumin.

Pedersen (1909) advocates the injection method for aborting gonorrhœal urethritis in its early stages, and says that it will also shorten the subsequent course of the disease unless a complicating sequel of antecedent urethritis is present, such as a stricture, for example. He favours the silver compounds argonin, protargol, albargin, argyrol and novargan. The injection of two drachms of a 2 per cent solution is given by a hand syringe every three hours on the first day and every four hours afterwards. The injections are retained for five to ten minutes. As the gonococci disappear he reduces the strength of the solution and the frequency of the injections to twice daily. After the gonococci have been absent from the specimen from three to seven days (according to the severity of the case) the injections are reduced to once daily, and stopped in from five to ten days later. If the inflammation is very acute the anterior urethra should be flushed with a 1 in 30,000 solution of perchloride of mercury before each injection of silver. He follows up the abortive treatment with astringent lotions.

Christian (1909) considered that injections of the newer organic silver preparations offered a reasonable chance of aborting gonorrhœa without producing the urethral irritation resulting from nitrate of silver, provided that they were employed early enough. He points out that these preparations must be freshly prepared, as they have little effect when seventy-two hours old.

Wossidlo (1909) advocates urethral injections of a solution of 1 in 2000 of albargin into the anterior urethra only. The patient carries out the treatment himself and injects the solution from four to six times daily, retaining it each time for five minutes.

Wyeth (1916) emphasises the importance of abortive treatment in general, in that a large proportion of cases of acute uncomplicated gonorrhœa, if seen within twenty-four hours after the discharge has commenced, can be cured in from five to six days—excepting

cases of primary infection. In criticism he says that the term "abortive treatment" as used in the text-books appears to mean the injection of some strong and highly irritating antiseptic, such as silver nitrate or mercury bichloride, after having anaesthetised the urethra. He is strongly opposed to the use of lotions in a strength at which they exert an astringent effect, and illustrates the remark in the case of Neisser's own remedy—protargol; saying that in a quarter to half per cent solution it produces a discharge from a normal urethra identical with that of gonorrhoea, minus the gonococci; whereas in a 2 per cent solution it is astringent. Nothing, he says, is contra-indicated more positively than the prevailing use of astringents—which, by their constricting effect upon the mucous membrane and blood-vessels, hamper rather than assist Nature's process, and thereby predispose to complications and chronicity.

His own method consists of successive flushings of the anterior urethra by means of a Janet-Frank syringe fitted with a Wheeler nozzle, using 300-450 c.c. of a quarter to half per cent solution of protargol according to the intensity of the inflammation. The anterior urethra is successively filled and then allowed to empty itself until the whole of the amount of the solution is used up. He prefers a hand syringe, to avoid "the undue pressure of an elevated irrigator." The patient is instructed to inject his urethra with the same lotion every four hours with a syringe of at least two drachms capacity, retaining this quantity for three minutes for two consecutive injections. The initial flushing is repeated when the patient reports on the second day; preferably he should report for same twice daily.

Frequently no gonococci are detected on the second day, but if a few are seen he is not discouraged as to the possibility of a cure being obtained in five to six days. If no gonococci are found after the third day the frequency of the self-injections is decreased. They are discontinued after the fourth day, and the patient kept under observation. If he remains free the case is said to have been aborted. If, on the other hand, gonococci are still detected, treatment is reinstituted and checked by the microscope. By continuing such treatment he states that no harm is done and the duration of the attack is limited to from three to six weeks, instead of the usual six weeks to three months.

With the above technique Wyeth claims 60 per cent of successes.

The writer has described this method in some detail, since it is a good example of the various schemes devised under "injections," in which the patient carries out the intermittent treatment at home. The majority of workers who employ the injection method in abortive treatment emphasise the following points:—

- (a) Extreme importance of commencing treatment within the first twenty-four hours.
- (b) Danger of using the solutions too strong, or forcibly.
- (c) Primary cases are more difficult to abort.
- (d) Results should be checked constantly by the microscope.
- (e) The technique should be such that, in the event of its being unsuccessful in aborting the attack, it will not have increased its duration either by necessitating a rest from all local treatment or by the production of complications.
- (f) The instructions given to the patient with regard to rest and dietary (see Wyeth's original article).
- (g) Importance of keeping the patient under observation for some time after the apparent cure.

Paul Asch says that it must occur to the mind of everybody that if we get the case early enough it might be possible to kill the gonococci by cauterisation or by injection of concentrated solutions of silver nitrate or protargol (2-20 per cent), and thus achieve an abortive treatment in a few days. He says that he has been far from pleased with results in cases so treated, and has accordingly abandoned it. He has seen too many cases dismissed as cured by such measures, presenting not only a discharge containing gonococci, but with a violently inflamed urethral mucosa, or even an incipient stricture.

Further treatment and ultimate cure have been delayed thereby. With other workers he agrees that—

- (1) The first requisite of a good abortive treatment should be that it does not irritate the mucosa too much, still less destroy it, and that it should permit of a possible transition to regular methodical treatment if unsuccessful.
- (2) An abortive treatment should be attempted only when the urethral mucous membrane does not show signs of severe inflammation, which signs he enumerates.

He describes his own procedure as the "*argyrol method*," which is only to be applied in appropriate cases, and which is harmless and successful with remarkable frequency. He prefers argyrol to the other silver preparations, since it is well tolerated by the urethra without pain, even in very concentrated solutions (20 to 40 per cent). Its only disadvantage is its high price.

Technique.—After urination, the anterior urethra is washed out with one pint of quarter per cent argyrol from an irrigator. This is followed immediately by an injection of one to one and a half drachms of a 12½ per cent solution, which is held in for five minutes by nipping the meatus. A few drops of this solution are allowed to trickle out each minute to ensure that the mucous membrane adjacent to the meatus is not neglected. After five minutes have elapsed the bulk is allowed to escape, but care is taken not to squeeze the urethra in order that a considerable quantity may remain adherent to its walls. He rigidly restricts the intake of all liquids, so that a pad of cotton-wool, which is worn to preserve the linen, need only be changed every twelve hours, when the patient also micturates prior to his next treatment. These weak irrigations, followed by the strong injections, are given every twelve hours for the first three days. After the third day the irrigations only are used, and are reduced in strength to 1 in 1000 or even to 1 in 2000. When the abortive treatment is successful, gonococci are not found in the specimens after the second day. If they are still detected, the abortive treatment is considered to have failed, and a regular methodical course is commenced at once.

Under the title of "Attempts to abort acute gonorrhœa in the male" the following technique is described by Edwards (1918), which the writer has decided to abstract as a good example of some of the drastic procedures which have been advocated. Edwards first states that 60 per cent of primary infection cases present a congenitally narrowed meatus; he therefore proceeds to do a meatotomy in such, under a local anæsthetic. The increased pain on urination following the above is considered slight, and is overcome by immersion of the penis for twenty minutes in water which is maintained at a temperature as hot as can be borne. Deeper obstructions, should they exist, must also be operated upon. [Irrigation with weak 1 in 4000 to 1 in 6000 potassium permanganate in acute gonorrhœa was only resorted to when the discharge was very profuse and the inflammation unusual, and he considers the benefit therefrom is due to the hot water.] After micturition the urethra is washed out with hot sterilised water to clear the mucous membrane and cleanse the field. An anterior urethroscopy is now made, the tube being carried down beyond the "point of infection." The membranes are observed for a distance of from three to six inches to be in a more or less highly inflamed condition with some pus oozing. [This might be anticipated!] After sponging away the pus, all points of infection are thoroughly swabbed with 20 to 40 per cent silver nitrate as the urethroscope tube is followed out and expelled from the urethra. These direct treatments to the mucous membranes are resorted to at intervals of from forty-eight to seventy-two hours, not exceeding a total of three or four. The immediate effects are increased discharge for twenty-four hours, slight increase in inflammation, and increased pain on micturition and erection. This additional irritation is also controlled by hot bathing, and the following treatment is administered six hours later. After micturition the urethra is cleansed with sterilised hot water, and two drachms of 1 per cent picric acid are "thrown into the urethra" with a glass "air pressure" syringe and held in for two to three minutes. Immediately after

expelling the picric acid, two or three drachms of a freshly prepared 60 per cent solution of argyrol is instilled deeply into the urethra and retained for five minutes. The instrument used for this was a "solid piston four-drachm metal syringe" with a long curved tip with a beaded point—the tip similar to that of the ordinary silver catheter. The above was repeated twice every twenty-four hours for from forty-eight to seventy-two hours, when the silver nitrate application (20 to 40 per cent) was again resorted to as the individual case demanded. In addition, the instillation of the 60 per cent argyrol was also repeated for as long as the inflammation or discharge remained. Upon the third or fourth urethroscopy the membrane showed a decidedly less inflamed condition—the silver nitrate was discontinued, and in its stead a freshly prepared full strength paste of argyrol was smeared on the membranes by means of a swab through the urethroscope tube, and left to absorb slowly.

Acute inflammation disappeared and the membranes resumed their normal appearance; the picric acid was stopped, but the argyrol continued at full strength.

The above schedule of treatment was administered to a series of 40 cases. All applied for treatment within six days from the commencement of the attack; 60 per cent in the first forty-eight hours, 20 per cent in seventy-two hours, and the remainder before the sixth day. In 32 only was the gonococcus detected. All the above cases disappeared from observation with the exception of nine who were watched from two to three months. (This is significant.) Three developed orchitis. Five were discharged on the eighth day and the remainder on the twelfth, excepting the three with orchitis, who were discharged on the eighteenth to the twentieth day. In 80 per cent of the cases mixed "Neisser Bacterin" was injected on the first day and repeated in from thirty-six to forty-eight hours until all reactions ceased. No test of cure is mentioned.

Loeb (1919), in a paper on the abortive treatment of gonorrhœa, says that he has obtained much better results by supplementing the local treatment with an intensive course of gonococcal vaccine. He states that he succeeded in aborting the disease with injections of 10 per cent protargol in 41 per cent of suitable cases, and in a further 24 per cent the disease, though not actually aborted, could be cured very much more quickly than usual. In a parallel series of cases in which he employed in addition an intensive course of intramuscular injections of "extra strong" arthigon, the successes were increased to 59 and 22 per cent respectively (together 81 per cent). The technique he employs consists in disinfecting the glans and preputial sac with 5 per cent silver nitrate, after which a urethral injection is given consisting of 5 c.c. of a 10 per cent solution of protargol diluted with 10 c.c. of 2½ per cent cocaine, which is held in for ten minutes. The above solution he says will keep for some weeks. The injection is followed by another of undiluted 10 per cent protargol, which is retained for ten to fifteen minutes. These injections are superintended by the medical officer, and care is taken that the fossa and meatus are not neglected. At the commencement ½ c.c. of "extra strong arthigon" is injected intramuscularly. Five to eight hours after the first injection, preferably on the same evening (otherwise the following morning) the 10 per cent protargol is injected and retained in the same manner. In the majority of cases the gonococci will have disappeared from the discharge on the second day, but should be looked for also on the third day to make sure. The injection is repeated on the evening of the second and third day, but in weakened solutions (5 to 2 per cent). The discharge on the third day is usually serous or sero-sanious, and generally contains chiefly leucocytes and no gonococci. The arthigon injection is repeated on the third day, when 1 c.c. is given, and 1 c.c. on the sixth and ninth day if the discharge still shows gonococci. The patient injects himself two to three times daily after the third day, using ½ to 1 per cent protargol. If he is not clear by the ninth day the above course is repeated. Loeb also described his method of aborting the infection in the wife. His successes have been obtained in cases where coitus has occurred while the husband's infection was yet in the incubation period. He gives first a douche of 1 in 500 sublimate solution, then the portio vaginalis and vulva

are thoroughly swabbed with 10 per cent protargol, and the same is instilled into the urethra, followed by insertion of a protargol tampon into the vagina. This measure has succeeded in a good number of cases, even in pregnant women, but he has been unable to abort the infection in a female in whom the existence of gonococci has already been proved. He thinks, however, that even in these cases "arthigon" should increase the chances of success. He concludes :—

- (1) The sooner treatment is commenced the greater the chance of success.
- (2) Patients who have suffered several times from the disease have a better chance than primary infections.
- (3) The microscopical appearance of the discharges cannot form the basis of the prognosis of the case.
- (4) A combination of arthigon vaccine increases the percentage of successes.
- (5) The possibility of preventative treatment in the wife must not be lost sight of.

Harrison in 1919 quotes a statement made to him by Lt.-Col. Raffan of the A.A.M.C., namely, that in a period of six months a total of 2600 cases of gonorrhœa were aborted at the eighteen centres established by the Australian authorities in this country for the abortive treatment. Raffan agreed with Ballenger in expecting 90 per cent of successes if the treatment commences on the first day—success meaning complete cure in a week to ten days. Encouraged by the success of the colonial medical authorities, an abortive centre was instituted adjacent to Rochester Row Military Hospital for Imperial Troops in the London District, but Harrison did not find that the results showed the high percentage of successes claimed by the Australians. He attributes this to the fact that nearly all his cases failed to attend until the second or third day. Thus out of 738 cases of gonorrhœa reporting at this centre in a period of four months, only 129 were considered worth the attempt at abortion. Of these, in 69 the attempt failed and they were admitted to hospital; 10 failed to complete the period of observation and so cannot be reckoned cures or failures, and 50 were successfully aborted in seven to ten days. In all, the diagnosis was verified by microscopical examination of specimens, and the cure was claimed on a negative examination after an interval of one week after cessation of all treatment.

Technique.—Many methods were employed, including iodoform bougies, large irrigations with potassium permanganate, and Ballenger's method, in which 20 minims of 5 per cent argyrol were sealed in the urethra for six hours. The latter proved fairly successful, but the majority of the cases were too far advanced to justify its application. Most of the cases were treated as below.

- (a) The parts are disinfected thoroughly with 1 in 2000 perchloride of mercury solution.
- (b) The urethra is irrigated with about two pints of 1 in 4000 pot. permang. solution, using a two-way nozzle.
- (c) Ten per cent argyrol or 5 per cent protosil solution is injected into the urethra and retained for twenty minutes.

This is repeated twice daily for three to four days, and then the silver compound is omitted and the irrigations continued for another four to six days. Specimens are examined for gonococci every other day. When none are detected and when the discharge is scanty, treatment is omitted for one day. If by the tenth day the urethra seems to be perfectly quiet, treatment is stopped, and the patient is told to report again in a week for confirmation of the cure. Should he return with a discharge he is admitted to hospital and considered as a failure. In such instances the abortive measures are not detrimental to the future progress of the patient, as is so frequently the case after the more drastic methods advocated.

Harrison considers that the successes would have been considerably greater if treatment could have been commenced a day earlier.

Boyer, in his method advocated in March 1920, seeks at first to bring about a profuse

exudation which carries the gonococci to the surface of the mucous membrane, and he then uses an antiseptic injection. The treatment must not be begun later than the third day of the discharge.

Two solutions are required :—

- | | |
|---------------------------|--------------|
| 1. Collargol | 1.50 gramme. |
| Glycerine | 30.0 c.c. |
| Distilled water | 250 c.c. |
| 2. Pot. permang. | 1 c.c. |
| Distilled water | 3000 c.c. |

The patient injects 10 c.c. of the first solution into the urethra by means of a small glass syringe, and keeps the meatus closed by pressing the glans between the left thumb and forefinger. The injection is held in the urethra for four to five minutes, after which the excess is allowed to run away and a small plug of cotton-wool is applied. The patient is then able to go about his daily work. At midday, after passing water, the patient again injects his urethra with a dozen syringefuls of the second solution. The last syringeful is retained for four to five minutes. At 2 o'clock another injection of collargol is given, and at 7 o'clock the urethra is again washed out with the permanganate solution. As a rule, after the third day, no gonococci are found, and the discharge itself disappears completely in from six to eight days.

With this method the patient can continue work, so that it is applicable to out-patients. Moreover, it is not likely to do much harm to the urethra. However, too much control is left in the hands of the patient, who is liable to discontinue attending unless he is given small supplies of the solutions. If he fails to attend, the physician is unable to know whether or not he has been cured.

Rosenthal (1921) advocates the following very simple technique for aborting gonorrhœa :—

First day.—An injection of 2 per cent albargin is made into the anterior urethra, and after a momentary retention with the nozzle, is expelled. This is repeated, and retained for a minute and a half, when the nozzle of the syringe is reapplied to the meatus, and, under somewhat greater pressure, a further quantity of the 2 per cent albargin solution is introduced, the anterior urethra being thereby fully distended.

(The compressor muscle probably having been put into a state of reflex spasm from the preceding injection, the anterior urethra will permit of greater distention.—C. H. M.)

The whole of the solution is now allowed to escape. The entire treatment should occupy only three minutes.

Second day.—The above is repeated, using the same strength of albargin, or in the event of irritation or negative findings of gonococci, is reduced to 1 per cent. The treatment is usually painless, but a preceding injection of 2 per cent alypin is sometimes necessary on the second day.

Third day.—If gonococci are detected the treatment has been unsuccessful, but no harm has been done and the patient is put on Janet's irrigations or some other routine treatment. If, on the other hand, gonococci are absent for the next ten days, the case is cured. That the cure is absolute Rosenthal is convinced, since he is not able to detect gonococci in such cures by his provocative test applied after an interval of twelve days. He claims that it is possible to determine within four days whether the gonorrhœal infection is still present and further treatment necessary, or whether any remaining symptoms are due merely to irritation. At least twelve days are allowed to elapse since the last treatment, and the prostatic secretions should be non-pathological before applying the following test :—

Rosenthal's Test of Cure.

- | | |
|--|--------------|
| Lugol's Solution : Tinct. iodid. | 20.0 c.c. |
| Potass. iodid. | 5.0 grammes. |
| Aq. destill. ad | 100.0 c.c. |

This is diluted five times and injected into the urethra on four successive days, being retained for three minutes. In sensitive persons the fluid is only retained for one and a half to two minutes before looking to see if the mucous membrane has been coloured reddish-blue, which is an indication that the action has been sufficient. The fluid expelled from the injection on the second and third day must be very carefully examined, since a few intracellular gonococci from old gonococcal "rests" may be found at this time, whereas on later days they may not be demonstrable. If after each of the four provocative injections no gonococci are found, he states that infectivity may be positively excluded. In cases of "catarrhal" urethritis, apart from the diagnostic value of this test, he has known these injections to clear up such a discharge which may have persisted for years.

Fuchs (1922), writing upon the dangers of the abortive treatment in gonorrhœa, emphasises the fact that careful discrimination is essential in selecting the cases to which it is applicable. Also extreme care should be taken with regard to the strength of the solutions employed. His experience appears to have been limited chiefly to urethral injections of albargin. He described two cases from his clinic, in one of which the use of 4 per cent albargin was followed by an impassable stricture four months later, and in the other a troublesome stricture also developed three years after similar treatment. He now never uses a solution of albargin stronger than 2 per cent for abortive treatment, and has never seen any stricture formation subsequently. For some time after receiving abortive treatment he encourages every patient to remain under observation, and to be repeatedly examined by the passage of soft, olive-headed bougies. If any infiltration is detected, a regular course of dilatations should be promptly instituted.

Injections applied through a soft Rubber Catheter.—As an example of this method, which is now hardly ever used, the writer would like to mention that advocated by Cabot (1901). He only applied this treatment during the first forty-eight hours of the discharge. After flushing out the urethra with hot water, a soft catheter is passed down to the bulb, through which is injected 5-8 c.c. of 10 per cent argonin. In order to retain as much of this solution as possible the meatus is nipped whilst the catheter is withdrawn. After an interval of five to ten minutes, a mounted swab soaked in 10 per cent argonin is passed down to the bulb and back to ensure all parts of the mucous membrane coming under the influence of the antiseptic. Any remaining fluid is allowed to escape. This treatment is repeated twice daily, increasing the strength of the solution until 30 per cent is reached. All solutions of this silver preparation are freshly prepared. He claimed excellent results.

In recent times there is an increasing tendency for any of the methods which necessitate any instrumentation within the urethra in the abortive treatment of gonorrhœa to drop into disuse.

The "Sealing-in" Method.—Probably the best known and most adopted method coming under this category is that devised by Ballenger, who originated the "sealing-in" process. It forms the basis of the several modifications which subsequently have been advocated by other workers. Only in exceptionally mild cases is this method applicable at a date later than forty-eight hours after the commencement of the discharge, and there is a very much greater chance of success if it can be commenced on the first rather than on the second day. The penis is cleansed, and in sensitive patients the meatus anæsthetised by laying across it a piece of cotton-wool soaked in 10 per cent cocaine. Thereafter, twenty-five minims of a freshly prepared solution of 5 per cent argyrol are injected and retained by gently squeezing the meatus between the forefinger and thumb. The meatus is then carefully dried and painted over with flexible collodion, the pressure not being relaxed until the dressing has dried. Gauze may be used to facilitate the removal of the collodion, which is carried out six hours later, either by dissolving with acetone or by pulling away the gauze. The patient is then allowed to urinate. The argyrol is sealed in by this procedure for six hours daily on five consecutive days. The discharge is examined for gonococci each day, and they are usually found to be absent on the third day. If they are still present on the fifth day, the sealing-in process is

abandoned, and the usual systematic treatment for gonorrhœa is substituted. The patient should drink water copiously until four hours before the occlusion of the meatus on each day. Ballenger claims to have aborted the disease by this method in from three to six days in a total of 750 cases, and he states that he can obtain 90 per cent of cures when all conditions are favourable.

McDonagh uses 1 in 2000 colloidal silver instead of the argyrol. He considers that the former is less irritating and equally efficacious; moreover, as it keeps well there is no need for immediate preparation.

Harrison (1918) has used the following slight modification of Ballenger's method with very successful results. After urinating, 20 minims of a 5 per cent solution of argyrol are injected into the urethra and retained by compressing the urethra behind the glans. After thoroughly drying the meatus some flexible collodion is brushed between the lips, which are then brought together again. The meatus is further sealed with three more coats of collodion, which are allowed to dry successively. The urethra is now very gradually released, and the penis is kept in the erect position. The solution is thus retained for at least four hours. This treatment may be repeated on three successive days, and may be followed up by daily irrigations with potassium permanganate for a further five days.

Bayly (1921) recommends "sealing-in" 30 minims of collosol argentum (Crooks) for three hours on two occasions on the first day, with an interval of six hours between the two treatments. For the next three days an anterior irrigation of 1 in 3000 potassium permanganate is given in the morning, and the "sealing-in" process is repeated once in the evening only. For the next five days the patient irrigates his anterior urethra morning and evening with 1 in 4000 potassium permanganate, using not more than a two feet "head" of pressure. On the tenth day he is examined bacteriologically, having had no treatment for twenty-four hours, and after having held his urine for four hours.

Irrigation Methods.—There are still a few workers who prefer to use a large syringe rather than the gravity method for the purpose of flushing out the anterior and posterior urethra. The reason they give is mainly based on the assumption that more harm is liable to accrue from irrigation by gravity. They claim that the sense of touch as applied to the piston of a syringe is more delicate than can be exerted in controlling the flow through the tube from an irrigator. The writer is not in agreement with this view, and submits that it is far easier to maintain an even, gentle, interrupted or continuous flow from the large reservoir of an irrigator—the height of which can be varied through a range from zero to say four feet. In addition to this control over the constant maximum head of pressure, one also possesses a further check on the flow through the tubing, held between the finger and thumb, capable of the finest adjustment. The nozzle can be applied so as to make a water-tight junction with the meatus, or to permit of a return flow, or to alternate the two. With the irrigator the pressure is supplied by gravity and one has only to regulate it, whereas with the syringe one has both to supply and regulate.

So numerous and varied are the drugs which have been employed from time to time throughout the civilised world for the purpose of irrigation that it is very significant to find one of the oldest still the most universally used for routine work. **Potassium permanganate** is still our most valuable drug for urethral disinfection from the gonococcus, such disinfection being brought about by copious irrigations with weak solutions. Janet in 1892 was the pioneer of urethro-vesical irrigations, which he performed without the use of a catheter, and his method rapidly became popular. In the earlier attempts to abort gonorrhœa by this means, the strength of the solutions of potassium permanganate which he advocated proved too irritating to the mucous membrane for the patient to tolerate. Janet soon modified his technique, of which a table is given below, similar to that appearing in Luys' text-book.

Day.	8 a.m.	Noon.	9 p.m.
1st	..	Ant. irrig. 1 in 1000	Ant. irrig. 1 in 1000
2nd	Ant. irrig. 1 in 3000	..	Ant. „ 1 in 4000
3rd	Post. „ 1 in 2000	..	Post. „ 1 in 4000
4th	..	Post. irr. 1 in 2000	..
5th	Post. irrig. 1 in 2000	..	Post. irr. 1 in 2000
6th	..	Post. irr. 1 in 2000	..
7th	..	Post. „ 1 in 1000	..
8th	..	Post. „ 1 in 1000	..
9th	..	Post. „ 1 in 1000	..
10th	Ant. irrig. 1 in 1000	Post. „ 1 in 1000	..

Luys has obtained good results with this method, but emphasises that it is only applicable within forty-eight hours after the commencement of the discharge, and then only in the absence of severe or painful symptoms. If commenced within the first twenty-four hours it gave 87 per cent of cures, but on the fifth day only 11 per cent.

In the writer's experience the strength of the solutions is excessive. Only in the exceptional cases can the schedule be adhered to, and then only at great inconvenience both to the patient and surgeon.

As an example of the abortive methods in which silver nitrate was used in massive irrigations might be mentioned that of Engelbreth (1904) of Copenhagen. His technique is described by Luys as follows:—

If the infection is taken within the first three days, the anterior urethra is irrigated with 500 c.c. of $\frac{1}{4}$ to $\frac{1}{2}$ per cent solution of silver nitrate at body temperature. Four such irrigations are given at intervals of approximately twelve hours, and the whole treatment is completed in forty-eight hours. This abortive treatment is only to be attempted within the time stated, in cases in which the meatus is not inflamed and the urine in the first glass clear, apart from flakes. Engelbreth claims great success in that 85 per cent of his cases were cured.

Berg (1905) relates his experience of the abortive treatment in 47 cases. Two or three irrigations of a silver nitrate solution of 1 in 500 at intervals of ten to fourteen hours were frequently sufficient to cause disappearance of the gonococci. In 67 to 78 per cent of the cases the treatment was successful. The presence of posterior urethritis, of inflammation of the external meatus, and the longer duration of the gonorrhœa than two days, are contra-indications.

Magian (1911) elaborated a somewhat cumbersome and complicated method for the rapid cure of gonorrhœa, which he claims can be achieved in one week, provided the treatment is commenced early. An extract of his paper appears in the Medical Annual (1912), from which these brief notes are taken. The steps are as follows:—

1. Anterior irrigation with 3 gallons pot. permang. warm (1 in 5000).
2. Anterior irrigation with 3 gallons distilled water warm.
3. Anterior irrigation with 3 gallons cold distilled water containing one ounce of protargol and with sufficient pressure to distend the mucous membrane.
4. Anterior irrigation with 2 pints of gold chloride solution (15 grains to pint), followed by washing out with distilled water. This irrigation is done with a single-way nozzle—the others with a two-way nozzle.
5. Injections of $\frac{1}{2}$ per cent protargol, eight to ten times during the next twenty-four hours by the patient himself, followed by the insertion of a six-inch Neisser bougie (1 per cent protargol and 2 per cent antipyrin), which is tied in at night.

Allosan tablets are taken three-hourly during the day. The irrigations are repeated in increasing strength on the second, third, and fourth days. On the fifth day an irrigation of weak zinc sulphate solution is given, and on the sixth, weak silver nitrate. The strength of the

last irrigations is varied with the severity of the case. After all this, the cure is said to be almost invariably complete. This author has used such treatment in 100 consecutive cases, and in only three was the cure delayed beyond the seventh day. He attributes his success to the large quantities of moving fluids under pressure and to their sequence. However good the above method may be, the cost in time and material alone renders it impossible for hospital, doctor and patient.

Wyndham Powell (1914) was one of the earlier advocates of urethro-vesical irrigations with potassium permanganate in this country. In a later publication he recommends that the whole of the anterior urethra be irrigated with full pressure (six feet head) in the early stage when only the first two to three inches are affected. The urethra should be ballooned with the fluid and then rapidly emptied. He considers that the resulting over-distension followed by the rapid collapse of the elastic urethra facilitates the entry of the solution into the orifices of the urethral glands and lacunæ. He prefers the single-hole nozzle, since with the two-way nozzle this distension is sustained with a probable stagnation of the fluid in the bulbous urethra. Another object is to set up a barrier to the spread of the gonococci in the form of a section of the urethra treated with potassium permanganate. He considers that irritating solutions such as silver nitrate, by lowering the resistance of the mucous membrane, facilitate the local spread. The strength of the solutions which he favours ranges from 1 in 5000 to 1 in 2000, using five or six pints at a temperature of 98° to 100° F. For the first three or four days he gives a morning and evening irrigation with a 1 in 3000 solution, followed by daily irrigations of 1 in 2000. Powell considers that if this treatment fails it is due to persistence of the infection in the lacunæ of Morgagni and Littre's glands, and is attributable to the treatment having been commenced too late.

In the opinion of the writer the following methods recommended by Wyndham Powell justify a detailed description :—

1. The time since the exposure and appearance of symptoms is ascertained.
2. The urethral smear is examined microscopically.
3. The patient compresses his urethra 2 ins. from meatus, whilst an irrigation of two pints of sterile water (temperature 98° F.) is given to this depth.
4. Patient again compresses his urethra behind the scrotum, and the above irrigation is repeated.
5. The whole of anterior urethra is likewise irrigated and well "ballooned," but care is taken to avoid the water entering the posterior urethra.
6. Patient now urinates into a clean glass, and the specimen will furnish rough information as to the extent of the infection. The previous washing should also be examined with this object.
7. If seen within a few hours of initial symptoms, and in the absence of evidence that more than the anterior 2 ins. are affected, an instillation of a solution of silver nitrate is made from an eye-dropper into the anterior 2 ins., whilst the patient compresses the urethra at this level. This is repeated six or eight times.
8. If the disease is more than a few hours old the silver nitrate must be used only subject to the amount of the local inflammation. Provided there are no shreds from below the first 2 ins., and it is not the first acute attack, the silver may be used up to the end of the first thirty-six or forty-eight hours.
9. In these cases he treats the anterior 2 to 2½ ins. with 1 to 1½ per cent silver nitrate, followed by an anterior irrigation with two pints of 1 in 2000 potassium permanganate.
10. Twelve hours later potassium permanganate irrigations should be commenced after examination of specimens to find if the silver has been successful. It is not unusual for one strong irrigation to cure even when gonococci have been found after the instillation of silver nitrate. The silver nitrate should but very rarely be repeated, and never be applied to the whole of the anterior urethra. His technique for irrigating is described elsewhere.

It is interesting to find Janet (1915)—that faithful adherent to potassium permanganate—describing an abortive treatment in which he uses an organic silver preparation. He

says that of the newer silver preparations, protargol and argyrol, he prefers the latter as being less damaging to epithelium. He believes that it is not too much to assume that it is possible to abort gonorrhœa in twenty-four hours, but provisionally he has adopted the plan of carrying the treatment over three days, usually two applications on the second and third days, but sometimes only one. The earlier in the first twenty-four hours of the disease the treatment can be commenced the better.

Technique.—After urinating, the anterior urethra is irrigated with half a litre of 1 in 400 argyrol. After the last drops of the solution have been expelled the anterior urethra is refilled, by an injection from a syringe, with 20 per cent argyrol, which is retained by nipping the meatus for five minutes. A few drops are allowed to trickle out from time to time, so as not to exclude the fossa from the action of the drug. On releasing the meatus the solution is allowed to ooze out, but care is taken not to squeeze the urethra, in order to leave as much of the argyrol on its walls as possible. A pad is applied now to the meatus and the patient advised to refrain from urinating as long as possible. If first seen before noon the patient receives another treatment the same evening, and again twice on the second and third days. Should irritation develop, the strength of the injection is reduced to 10 per cent or even 5 per cent. The first micturition after the first treatment is sometimes painful, but not often. Should the irritation become severe he is content to give only the irrigation at 2–3 in 1000. In every case that is cured the gonococci are not detected after the first treatment. Occasionally a few degenerated gonococci may be seen after such, and the case may yet become aborted. If gonococci are found after the second treatment one can be certain that the case will not be aborted, and he personally abandons the intensive treatment, immediately placing the patient on routine treatment with potassium permanganate.

Out of 98 cases treated by this method he obtained 47 cures. There were 56 cases out of the total in whom treatment was commenced within the first twelve hours of the symptoms appearing. With these he obtained 36 cures and 20 failures, *i.e.* 64 per cent of successes. In the remaining 42 who commenced treatment later than the first twelve hours he obtained 11 successes and 31 failures, *i.e.* 26 per cent of cures.

Bierhoff (1918) in his method of aborting gonorrhœa advocates a combination of anterior urethral irrigations and injections of protargol. Having satisfied himself that the case is a suitable one for attempting abortive measures, he proceeds as follows:—

First day.—Anterior irrigation, using 450 c.c. of $\frac{1}{2}$ per cent solution of protargol followed in four hours by an injection of 8 c.c. of a $\frac{1}{2}$ per cent solution of protargol containing 15 per cent glycerine, which is retained for ten minutes. The latter is repeated by the patient every four hours.

Second day.—Urethral smear examined, and if the cure is going to be a success there will be no gonococci detected (twenty-four hours after commencement of treatment).

The treatment is continued as on the first day.

Third day.—Morning discharge examined prior to any injections or urination should show almost exclusively epithelium and no gonococci.

Treatment.—One anterior irrigation with 300 c.c. of a $\frac{1}{4}$ per cent solution of protargol. The patient should inject himself only three times on this day.

Fourth day.—Should he be free of gonococci, the irrigation is omitted, and the patient injects in the morning and evening only.

Fifth day.—All treatment ceases, and the patient is told to try the alcohol test in moderation, and this is continued for a week. If specimens still show no signs of gonococci he is permitted to indulge in "coitus condomatus."

If gonococci are still absent from specimens the case is considered as aborted.

Results.—The total number of cases treated was 363, of which 63.6 per cent were reported free of gonococci after forty-eight hours' treatment, and of the remainder more than half were considered free of gonococci within three weeks.

Harrison (1918) suggests a combination of the "massive irrigation" and the "retained injection" methods thus: An anterior irrigation with 1 in 3000 potassium permanganate is followed by an injection of 4 c.c. of 10 per cent argyrol—the latter being retained for twenty minutes. The above are given twice daily for the first four days, and the irrigations are continued alone for a further five days.

Lumb (1918) advocates that irrigation with potassium permanganate 1 in 8000 should be commenced as soon as the condition is diagnosed, and every attempt should be made to get the fluid into the bladder. Two or three pints are used per irrigation, the temperature being 100° to 105° F.

He probably is alluding to cases who are in the post-abortive stage before treatment is commenced, since as contra-indications to the above he gives hyperacute urethritis or acute epididymitis. Much controversy has arisen as to the propriety of posterior irrigations in the treatment of anterior urethritis. The writer's views are entirely in accordance with the arguments set forward by Harrison in favour of urethro-vesical irrigations in this condition in a paragraph under the heading of "Anterior versus Anterior and Posterior Irrigations in Anterior Urethritis," which appeared in the *Lancet*, 1919, p. 220, and to which he would refer the reader.

With regard to the old method of irrigating the anterior and posterior urethra by first filling the bladder through a catheter after the withdrawal of which the lotion is passed naturally, this, for obvious reasons, has been abandoned long since as a method of aborting gonorrhœa.

Intra-urethral Dressings.—Various modifications have followed upon the original "urétro-mèche" method of Boureau (1897). As described in Luys' text-book this consisted of a wick of cotton-wool which was inserted aseptically into the urethra with a stilette after being impregnated with 1 in 1000 perchloride of mercury ointment. At the anterior end was attached a piece of string which acted as a guide during introduction, and afterwards was left hanging out of the meatus. The meatus was then covered with a piece of cotton-wool. The wick was retained for from three to seven hours, when it was washed away by the patient passing urine. It should not be pulled out.

Fogarty in 1917 introduced a modification of Boureau's "urétro-mèche" method to the Australian Army Medical Corps, which was termed the "massage pack" method. For the period 1917–1918 this method was advocated in preference to others for the early or abortive treatment of gonorrhœa by the Australian authorities, and accordingly it was applied to a large number of their military cases in this country.

The following very sound regulations were laid down in the orders for each abortive centre:—

1. Only those cases presenting the earliest signs and not exceeding twenty-four hours in duration were to be attempted.
2. A limited course (four to six days) of abortive treatment was scheduled in time-table form.
3. All cases not cured at the end of this time were to be sent immediately to hospital.

Technique.—

(a) After urination, the glans and preputial fold are cleansed with 1 in 8000 pot. permang. "A probe is introduced into the urethra to determine its general direction, and whether there is any narrowing or other obstruction" (of which the writer strongly disapproves).

(b) One end of a strip of gauze (1 in. × 7 ins.) soaked in 5 per cent argyrol is passed down to the compressor muscle on a bulbous-headed probe, the other end protruding from the meatus.

(c) The whole of the anterior urethra is now massaged against the pack for five minutes.

(d) The pack is withdrawn through the gently compressed meatus, as much argyrol being retained as possible.

(e) A second pack is introduced in the same manner and retained for four hours.

The above process is performed twice a day in the majority of cases—in some three times. The pack is rarely necessary after the fourth day, after which gentle irrigation with 1 in 5000 potassium permanganate thrice daily is substituted.

Results.—Out of 742 cases treated in ten months (in 1918) only 13 were sent on to hospital as “not cured” on or before the eighth day of treatment. Of these 13 there were 7 uncomplicated failures and 6 complicated (bubo 1, epididymitis 6).

At first sight these results appear to be extraordinarily satisfactory; but when we look through the test of cure we find sources for gross inaccuracies which might very materially alter the 98 per cent of successes shown above. For instance, with the first 498 cases so treated, cure was determined by absence of subjective symptoms, combined with a “dry urethra,” or “merely a thin watery secretion” observed on massage and expression in the early morning prior to micturition. The writer finds it hard to realise that out of all these cases there were only 13 unfortunates who experienced subjective symptoms at the time they were examined for cure. Each of these men had endured a foreign body for at least eight hours a day in his urethra, which, in addition, had been twice massaged against this foreign body on four days, followed by three irrigations a day. They truly must be a hardy race! But the “thin watery secretion” is more tangible; and when we read in the next paragraph that it was only in the remaining 244 cases, less than one-third of the total, that the cure was supported by the microscope, we are reasonably justified in becoming sceptical. In these 244 cases there were only 184 from whom the specimens were examined after staining by Gram’s method. However, 183 cases seem to have been examined more thoroughly, since they were kept under observation for nine days after cure, during which time specimens were taken on the third, sixth, and ninth days. Fogarty points out that he was unable to trace his cases for longer than twenty-four hours after reaching the *dépôt* to which they were sent, and most of them proceeded to France. He concludes that he is of the opinion that given a suitable speculum or introducer the posterior urethra could be treated to advantage in a similar manner. The writer has had no personal experience with this method, but he had many Australian soldiers who received anti-syphilitic treatment under his charge at Rochester Row Military Hospital with whom he was able to discuss the “massage pack” treatment. It appeared that some of the men were suspicious that there was an element of punishment combined in the treatment.

It is instructive at this point to look through a valuable paper on gonorrhœa written by Macky in 1920 and titled, “Some Notes on the Evil Results of its Abortive Treatment in the A.I.F.” This officer appears to have had great facilities for gathering his experience with regard to the after-effects of abortive treatment. Upon the sequelæ of the various abortive methods recently employed on a large scale the writer has been unable to find any record approaching that of Macky for comprehensiveness and urethroscopic detail. In discussing the strict orders issued to those in charge of the abortive centres (previously mentioned) which were organised in every camp, he writes: “*These measures were rewarded with a well-deserved success, according to the monthly figures compiled, and at certain periods only 3 per cent of cases treated had to be sent to hospital for further treatment. From the Army point of view this is a fine result. From the patient’s point of view (as will appear more fully later) it is not an unqualified success, and had a more stringent standard of cure been insisted on, I am convinced the cures would have dropped to more like 40 per cent than 97 per cent.*”

In describing the urethroscopic appearance in cases of failure after the “massage pack” treatment he writes: “*In my experience every failure after this treatment has shown on endoscopic examination the above described ‘tanning’ effect of argyrol to perfection (i.e. the anterior urethra back to the angle was palpable as a firm cord. Endoscopically it had the rigidity and appearance of leather, but was friable and bled freely unless handled with extreme care. It was studded with discharging follicles).*”

“*The difference is that the damage is limited abruptly to the area of contact with the*

plug—in effect, a tubular stricture one to two inches long which may be wide enough to admit an F.24 bougie, but is almost incapable of further dilatation. It is always the seat of an intense Littritis. Extension complications are commoner than in a series of untreated cases. I have twice seen peri-urethral abscess at the deep end of the stricture band. Gonococci can be found in the discharge from the inflamed glands of Littre when difficult to detect in meatal slides. The loop on a platinum cautery is a convenient instrument for obtaining these specimens. During subsequent dilatation the bands are prone to develop fissures in the floor of the urethra, or patches of granulation or polypoid formations at the deeper end."

In summing up his detailed description of the pathological changes he found in the "failure" cases, he states that the cases of confirmed gonorrhœa following attempts at abortive caustic treatment present certain features in common:—

- (1) Marked Littritis worse than that found in the average untreated case.
- (2) More or less serious damage to the mucous membrane, involving fibrosis and favouring secondary infections.
- (3) An increased incidence of extension complications.

He concludes thus: The attempt at rapid cure failed because disinfection of Littre's glands failed, and such methods must fail unless instituted before these glands become infected. Invariably the cases where abortive treatment has failed are worse and more difficult to cure than cases not so treated. Good results are claimed and have no doubt been obtained, but most careful selection of cases is essential, especially as regards the factor of the time that has elapsed since the onset of symptoms.

He found that the failures occurring after abortive treatment had been attempted by irrigation with potassium permanganate showed little beyond the common mild Littritis, and no mechanical damage to the urethra. He considers that this method has none of the drawbacks of the silver methods (injections of silver nitrate, argyrol "seals," "massage packs"); also that it is safe and can be used with advantage at a stage when rapid disinfection methods are too late to be attempted.

Instillation Method.—Feleki was one of the earliest advocates of applying silver nitrate to the urethra through the tube of an anterior urethroscope with the object of aborting an attack of gonorrhœa. Luys describes Feleki's technique thus. A urethroscopic tube is passed down to the bulb, and then as it is gradually withdrawn, the urethral mucous membrane is painted with a brush soaked in 5 per cent solution of silver nitrate, which has been inserted through the tube for that purpose. In very early cases with a barely noticeable secretion, one of these applications was sufficient to produce a cure. In others the treatment had to be repeated several times.

Medicated Bougies.—Antiseptics have been applied to the urethra by this means chiefly in dealing with chronic infections of the lacunæ and glandular orifices. Recently, however, medicated bougies have been used more extensively as a prophylactic measure against infection after exposure. The writer considers them as a valuable means of performing immediate self-disinfection, since they are easily carried in a small tin about the person of those frequently exposing themselves to venereal risks. There are some who favour the employment of medicated bougies in the abortive treatment of gonorrhœa, the insertion being made after a prolonged initial irrigation of the anterior urethra. A short account of the drugs most commonly applied in this manner is therefore appended.

In this country there are two bases commonly used to embody the required antiseptic.

(a) *Gelatin Base.*—These are made in two lengths, $2\frac{1}{2}$ ins. and 4 ins., and are inserted after being dipped in warm water. In America the lengths are $2\frac{3}{4}$ ins. and $5\frac{1}{2}$ ins.

(b) *Cacao butter* (*Ol. theobromatis*) has a melting-point of 88° to 93° F., which is below the temperature of the body. It is well to add 5 to 15 per cent beeswax if they are for use in hot climates.

These are cast in any length up to 6 ins. as required, and in six sizes ranging from $\frac{1}{8}$ of

an inch to $\frac{5}{16}$ of an inch in diameter. As with the gelatin base the American lengths are $2\frac{3}{4}$ ins. and $5\frac{1}{2}$ ins.

Klien (1920) favours the following base :—

Sacch. alb. subtil. pulv., 5·0.
 Sacch. lact.
 Pulv. gum. Arab., āā. 1·7.
 Pulv. tragacanth.
 Glycerin q.s.

To make 12 bougies 7 cm. ($2\frac{3}{4}$ ins.) long and ·4 cm. thick.

The glycerine and tragacanth are proportioned so as to render the bougie flexible without being too rigid.

He has employed the following preparations—protargol, ichthargan, caviblen, choleval and uranoben to the proportion of 10 per cent in the above base, but mainly in the female in the form of urethral and cervical bougies.

Iodoform Bougies.—

Iodoform. prec.	.	.	.	grs. v.	} to make bougie 4 ins. long.
Ol. eucalypti	.	.	.	℥x.	
Ol. theobrom.	.	.	.	grs. xxxv.	

Cheyne and Burghard advocate the use of the above, and it has produced good results in aborting gonorrhœa. It is more frequently used $4\frac{1}{2}$ ins. long, and in width equal to a No. 10 English catheter. Its insertion is facilitated by dipping the tip of the bougie in eucalyptus oil, after which it is introduced into the urethra as far as possible, and then a small meatal dressing is applied. The patient is made to urinate before the bougie is inserted, and the intake of fluids is restricted in order that the bougie may be retained as long as possible. It is better to maintain the penis in the erect position, and the patient should be instructed to refrain from moving about. The treatment is repeated only once after an interval of twelve hours.

Gonostyli contain 1 per cent of protargol and 0·1 per cent of ichthargan. These were given a fair trial in various clinics when they were first introduced but have gradually lapsed into disuse. Luys states that in his experience they have not given any appreciable therapeutic results in the abortive treatment.

Nargol bougies contain a nucleinate of silver in a strength of either 1 or 2 per cent mixed with a base which melts slowly at intra-urethral temperature. They have been used more as a prophylactic measure than in the actual abortive treatment of the established disease. (The writer has used the above, but in his experience they are too astringent in their action.)

Silver nitrate bougies containing $\frac{1}{2}$ grain of the drug in a cacao butter base have been tried, but are used more extensively in chronic anterior urethritis.

Thalline sulphate bougies, $2\frac{1}{2}$ ins. and 4 ins. long, containing 1-2 grains of the drug in a gelatine base have had their advocates, and also *Antrophores*,¹ or *spiral spring bougies*, are coated with gelatine and medicated with 10, 5, or weak ($2\frac{1}{2}$ per cent) of thalline. By this means the following drugs also can be applied—silver nitrate $\frac{1}{2}$ -3 per cent, iodoform 5, 10 and 20 per cent, protargol $\frac{1}{2}$, 1, $1\frac{1}{2}$ and 2 per cent, zinc sulphate $\frac{1}{2}$ per cent, etc. (The writer does not favour the use of antrophores, as the spring which remains acts as a foreign body.)

*Collapsubes*² are collapsible tubes containing ointments or creams in which are incorporated the drugs selected for application, with which are supplied a catheter attachment for urethral medication. As previously stated, the writer is strongly opposed to any method of aborting gonorrhœa necessitating intra-urethral instrumentation.

¹ See *Extra Pharmacopœia*, Martindale and Westcott, vol. i. (1920), p. 317.

² *Loc. cit.* p. 11.

Glycerine Ointment.—A valuable means of applying a drug to the urethral mucous membrane—more especially when one is desirous of producing serous exudation—is to incorporate such drug in a glycerine ointment. Hare's formula is recommended by Harrison, and contains one part of potato starch and one of glycerine. The application can be made by slowly injecting the ointment into the meatus from a collapsible tube or syringe with a wide aperture and nozzle.

As applied under the technique described when discussing iodoform bougies, that is, immediately following the initial thorough irrigation, one can see no valid reason why a drug thus maintained in contact with the urethral mucous membrane for several hours should not possess an excellent chance of aborting the infection. Undoubtedly the failures reported have been due more to lack of discretion in choosing the case suitable for the attempt than to the medicated bougie *per se*. If used within the first twelve hours of the established disease as the "follow-on" to a thorough irrigation (4 pints of 1 in 2000 potassium permanganate of 100° to 105° F., the last pint of which enters the bladder) the medicated bougie should more than recover its waning popularity.

Caution should be taken as to the strength in which the drug is applied by this means, so that, in the event of failure, routine treatment may be substituted immediately, without an enforced rest under antiphlogistic measures. Under these circumstances there is a minimum of risk of the production of mechanical damage to the urethral mucous membrane terminating in fibrosis. Theoretically the glycerine ointment, by virtue of its hygroscopic property, should be expected to assist the gonococcicidal action of the drug by ensuring its intimate contact with the cocci thus drawn into the open with the serum. Those gonococci which already had gained the protection offered by the lacunæ and gland orifices thus might be brought under the influence of the antiseptic and thereby be destroyed. Should the efficacy of this method become established, the simplicity of the technique would be appreciated by the patient and surgeon in comparison with that of some of the methods described above. In the writer's experience he has not found soluble bougies to be popular with patients, owing to their liability to soil the clothing and bed linen. This can be overcome by instructing the patient to cover the penis with a thick rubber sheath which will stand being boiled. The ideal time to insert a soluble bougie is "last thing at night" whilst the patient is in bed. In a clinic where beds are available for abortive treatment this could be accomplished.

Electrolytic treatment for the abortive cure of gonorrhœa has been advocated by Virghi.

Technique.—

1. Having urinated, the anterior urethra is washed out with sterile water.
2. Five c.c. of a 2 per cent solution of cocaine are injected and retained for a few minutes.
3. The cocaine is expressed and 5 c.c. of a solution of protargol (? strength) are injected and retained.
4. The negative electrode is introduced into the urethra, which still contains the protargol. This electrode consists of a flexible olive-headed metal bougie with insulated surface, and it is moved about in order that the head may come into contact with the whole anterior urethra.
5. The positive pole is placed on the body, and the current regulated so as not to produce smarting. The treatment lasts for three or four minutes, and is repeated in twenty-four hours.
6. After this the urethra is irrigated with boric lotion, followed in two or three days by massage on a straight sound, and the application of protargol or silver nitrate to the fossa navicularis through an endoscope. If the gonococci reappear in the discharge the electrolytic treatment is repeated.

Virghi claims 100 per cent of cures out of a total of 92 cases treated. In 57 cases the duration of the disease was from one to three days, and with these a cure was obtained in about eight days. He considers that this treatment may be successful up to the eleventh day after infection.

Abortive Treatment in the Female.—The initial stage of gonorrhœa in the female

is usually unaccompanied by signs or symptoms of sufficient severity to attract the patient's attention. Accordingly the disease is rarely diagnosed until the infection is established deeply. The majority of cases, therefore, in which the abortive treatment can be instituted at a date favourable to success are those voluntarily seeking advice soon after exposure. Frequently it happens that such exposure occurred with a male known to be suffering from gonorrhœa, or during the incubation period of his infection. Bierhoff insists upon microscopical examination of scrapings taken from the urethra, vagina, and endocervix, and in the favourable case proceeds with the following methods to endeavour to abort the infection.

Technique.—

1. The vulva, meatus, urethra and surroundings are cleansed and irrigated with $\frac{1}{4}$ to $\frac{1}{2}$ per cent solution of protargol.
2. About 150 c.c. of this solution is then introduced into the bladder and expelled by the patient.
3. A vaginal douche is given of the same solution, with which the vagina is thoroughly distended by compressing the outlet.
4. A sterilised speculum is inserted and the vaginal mucous membrane, fornices and cervical orifice are carefully cleansed with pledgets of cotton-wool.
5. If no gonococci have been detected in a specimen from the cervical canal the vagina is now packed with absorbent gauze soaked in 1 per cent protargol solution.
6. If the vagina has been found to be infected, 5 per cent protargol solution is used for this.
7. A soluble urethral bougie $1\frac{1}{2}$ ins. long containing 5 per cent protargol is inserted in the urethra.
8. A pad of cotton-wool soaked in 1 per cent protargol is placed over the urethral and vaginal orifices and retained in position with a "T" bandage. The patient abstains from passing urine for at least two hours. Rest in bed, bland diet, and a daily warm sitz bath are ordered.
9. After twenty-four hours the tampon is removed and the whole treatment repeated.
10. After two such applications, if no gonococci are detected, the urethral irrigation and bougie are omitted.
11. A bichloride of mercury solution 1 in 4000 or zinc sulphocarbolate solution 1 in 50 is substituted for the protargol as the vaginal douche, and the tampon is omitted. Such treatment is continued should any gonococci still be detected.

Saenger (1920) lays stress upon the importance of warding off an infection of the cervix. He states that the gonococci are usually limited to the urethra at first. In 96 out of 98 cases he found gonococci in the urethra, whereas they were present in the cervix in only 78. His description of two cases shows that by active means to save the cervix from infection it is possible to abort gonorrhœa. The patient is kept at rest. No vaginal douches are allowed. The external genitals are washed with an antiseptic. The urethra and para-urethral ducts are treated vigorously by the physician himself at least once a day, and the woman has to stay in bed during menstruation.

When a married man presents acute gonorrhœa, Saenger insists on his wife coming for examination and treatment, and by this means has often succeeded in aborting the infection in her.

Conclusions.—From amongst the literature the writer has selected examples of the different methods which have been devised from time to time for the abortive treatment of gonorrhœa. In this selection he has endeavoured to provide the reader with a fairly comprehensive review upon the subject from which to formulate his own ideas.

Less Drastic Measures.—On perusing the descriptions of the various techniques, one is pleased to observe a general tendency amongst the more modern workers to employ methods from which less damage, immediate and remote, is likely to result to the urethral wall. Surely some of the earlier "abortive cures" must have been worse than the disease itself. Caustic and markedly astringent lotions have fallen into disuse, as also

have methods necessitating intra-urethral instrumentation. Massage of the urethral wall against a foreign body, as in the "massage pack" method, will certainly ensure a thorough application of the accompanying drug, but it will also assist the gonococci in their progress along the lymphatics,¹ and in the depth of their intercellular penetration. The latter is evidenced by the diffuse sub-epithelial infiltration which is such a frequent sequel in cases so treated. There is one point emphasised by all the workers, namely, that the percentage of successes obtained by the various methods would be very much higher were they to include only those cases in which the attempt to abort the infection was made within the first twelve hours of the established disease. The whole question devolves itself upon this one absolutely controlling factor.

The Accessibility of the Gonococcus.—It would seem safe to assert that no method yet has been devised by means of which we are justified in guaranteeing to abort gonorrhœa if the gonococci have had time to penetrate into the gland orifices opening upon, or the intracellular spaces of, the urethral mucous membrane. If the case can be brought under treatment before this penetration has occurred, such is the susceptibility of the gonococcus to weak solutions of antiseptics, that in all probability one thorough irrigation with say 1 in 2000 potassium permanganate would suffice to abort every case. Personally, the writer believes that this penetration takes place earlier in the infection than would appear to be generally accepted. How else can we explain why the failures which follow early disinfection should increase with the time allowed to elapse since exposure? On referring again to Rigg's figures we see that the results from early disinfection, if applied within the first hour following exposure, were very satisfactory, up to the end of four hours moderately so, but from the fourth to the tenth hour there is a very heavy increase in the percentage of failures. In fact the 7·40 per cent of infections which occurred where the delay exceeded ten hours is estimated approximately as being equal to the average risk of infection from promiscuous exposure when *no* precautions are taken. If the gonococci during say the first twenty-four hours existed purely in the form of a surface colony upon the walls of the fossa navicularis, then theoretically, one thorough application of an antiseptic to the urethra within that period would be an infallible prevention against gonorrhœa. Unfortunately, clinical evidence contradicts this. Whilst discussing the accessibility of the gonococcus it is interesting to note a clinical observation made by some of the workers, namely, that if gonococci are detected in specimens on the morning after the first attempt at thorough disinfection of the urethra the case subsequently will not be successfully aborted by further measures.

Time Limits.—Many of the modern workers are of the opinion that only under exceptional circumstances should abortive measures be attempted when more than twenty-four hours have elapsed since the first symptoms. It is certain that had such a rule been adhered to in the past, the abortive treatment would have stimulated less adverse criticism amongst both the profession and patients.

Almost without exception every writer expresses his confidence in being able to show a much higher percentage of successes if he were to include only those cases in which treatment was commenced on the first day. Some of the French and German surgeons go further and divide this period into the first and second twelve hours, as opposed to the lax classification of others who loosely describe their results in "second and third day cases." As we have shown in the early paragraphs of this chapter, the rate of progress of the infection is controlled by local and general influences and varies considerably with the individual.

Discretion in selecting Cases.—Clinical experience is extremely important in discriminating in which cases one is justified in attempting abortive treatment. The time factor, if alone relied upon, frequently would lead the inexperienced to set out upon a therapeutic campaign which a wider clinical experience would have told him was bound to end in failure. It is upon the clinical findings at the first attendance, therefore, that

¹ See reference at end of Chapter.

the decision should be made, and not upon the history given by the patient. Again, the conditions under which the patient lives, his occupation and the distance he may be forced to travel for the subsequent visits, should be considered. The best results will be obtained always if the patient can be placed in bed for at least three or four days on the commencement of the abortive treatment.

First Infection Cases.—It has been mentioned frequently that cases of first infection are refractory to abortive measures. The blame is placed upon the vulnerability to the gonococcus of the virgin cylindrical epithelium in such cases, as opposed to the resistance of the pavement epithelium which, to a large extent, replaces the cylindrical in a urethra which has been diseased previously. In the writer's experience, however, it is very unusual for a patient who has contracted gonorrhœa for the first time to seek medical advice as promptly as those who, having had the disease before, appreciate the importance of immediate treatment. Moreover, a patient who has suffered previously is more apprehensive after exposure, and is also familiar with the earliest symptoms, as compared with the novice. The latter, from inexperience, shame, and even fear, hopes against hope until urged by the advice of friends, or the local discomfort, to seek treatment. It is therefore rare for a primary infection case to report sufficiently early to justify an attempt to abort the disease. The youth and ignorance of the individual in some instances might be apt to persuade the surgeon to take a risk and attempt to abort the attack—where judgement would have overridden sympathy in the case of a hardened sinner.

When to Abandon the Attempt.—We have seen that some writers have stated that should gonococci be detected in the morning specimens following upon the initial application of the treatment the case will not be successfully aborted. The majority of workers, however, persist until treatment for three days has been proved ineffectual—as evidenced by the presence of gonococci, and some even will continue over the fifth day in the absence of signs of irritation. The local reactions most frequently met with, any of which will necessitate a cessation of the intensive urethral treatment, are swelling and œdema, hæmorrhage, retention of urine, epididymitis and epididymo-orchitis (not infrequent in the "sealing-in" methods). Cystitis and acute prostatitis are of rarer occurrence. As stated above, these results of irritation are less liable to develop if the patient be kept in bed, well purged with salines, made to drink copiously, the urine rendered alkaline, and rectal suppositories containing glycerine and belladonna inserted morning and evening.

The Dangers of Abortive Treatment.—The risk of the causation of any of the foregoing complications should be borne in mind and guarded against. The enforced cessation from local treatment, should any such conditions develop, permits of a rapid extension of the infection upon tissues damaged by excessive mechanical interference. There is, undoubtedly, a marked tendency for the development of urethral sub-epithelial infiltrations, local or diffuse, in the patients who have been treated by even the milder forms of present-day abortive measures. Such cases require careful after-treatment with the object of promoting the absorption of such infiltrations with the minimum production of fibrosis. All patients who have been treated by abortive measures should be followed up, and therefore should be instructed in the importance of attending at such intervals as are indicated by the urethral condition. Only by this means can stricture formation be anticipated and dealt with if necessary by dilatations. Urethroscopic examination is absolutely essential to accurate diagnosis and prognosis in these sequelæ following abortive treatment. In cases in which the abortive treatment has failed, whether this is determined at the time, or subsequently by a relapse, there is frequently present a very intractable infection of Littre's glands with much peri-glandular infiltration. Peri-urethral abscesses are not infrequent in this condition.

The Selection of a Method.—The following are the main essentials to be taken into consideration in endeavouring to arrive at the ideal method for aborting gonorrhœa :—

- (1) It should be capable of eradicating the infection in a minimum of time if applied in a favourable case.

- (2) Failing this, it should keep the infection localised and prevent the spread to the posterior urethra.
- (3) It should be such that routine treatment for acute or subacute anterior urethritis can be substituted without interruption.
- (4) A minimum of damage should be caused to the urethral mucous membrane.
- (5) The method should necessitate as little inconvenience to the patient and the surgeon as possible.
- (6) It should be capable of modification to comply with the exigencies of the patient.

The writer has stated previously that he is strongly opposed to any method necessitating intra-urethral instrumentation, or the introduction into the urethra of any foreign substance other than the solutions of drugs in a strength that is neither caustic nor astringent. His experience has been almost entirely confined to private cases, all of which he has kept in bed for about a week. He has abandoned the "sealing-in" method, on account of the sequelæ mentioned above, and at the present date considers the "massive irrigation" method capable of fulfilling more of the above postulates than any other. He has certainly seen less damage result from its employment than from any other method.

The Writer's own Method. Having decided, after the initial clinical and microscopical examination, that a patient has reported sufficiently early to justify an attempt being made to abort the attack of gonorrhœa, the writer proceeds as follows:—

The patient is made to cleanse his hands, external genitalia and surrounding parts thoroughly with a pinch of soft soap and a warm solution of 1 in 1000 lysol. The prepuce is withdrawn and the preputial sac, glans, penis, and meatus well disinfected—special attention being paid to each frenal angle. In the absence of any *sore* the parts are rinsed now with a 1 in 2000 solution of hydrarg. perchlor. or biniodide. (Should a sore be detected, however, mercurials are withheld locally whilst specimens from the same are examined daily by dark-ground illumination. The sore is kept dry by frequent applications of pulv. sulph. ppt. until it heals. Sulphur has no inhibitory effect upon spirochaetes but is excellent in healing a chancre.)

First day.—I. If possible the patient should now urinate.

(a) The patient is placed upon a couch or in bed and made to occlude his bulbous urethra by digital pressure applied behind the scrotum.

An irrigation is given to this level, using two pints of an **alkaline**¹ solution of 1 in 2000 **pot. permang.** as warm as can be tolerated. A five-foot head of pressure is employed for this. The patient having released his urethra, the reservoir is lowered now to three feet and a gentle flushing continued up to the compressor muscle with a further pint of the lotion. With a fourth and last pint the muscle is coaxed to allow about half that quantity to enter the bladder. The permanganate is then somewhat forcefully passed out by the patient whilst he gently compresses the anterior two inches of the urethra. After a rest of ten minutes any residual permanganate solution is gently "milked" out of the anterior urethra.

(b) Two drams (7 c.c.) of a freshly prepared 5 per cent solution of **cargentos** is injected into the urethra with a rubber-nozzle glass syringe, and retained for from ten to fifteen minutes. The patient keeps this solution in the urethra by laterally applied pressure to the meatus between thumb and index finger. A few drops of the cargentos are permitted to trickle through the meatus every two or three minutes to ensure that the walls of the fossa navicularis do not escape its influence. At the conclusion the meatus is released and the penis is maintained in the erect position by a pad of lint strapped to the abdomen. No attempt should be made to empty the urethra; on the contrary, by gentle manipulation as much cargentos is to be retained as possible. If the patient be kept in bed this may be feasible, but if he has to go about his business a dressing must be worn to protect his clothes from stains. In either case he should be told to refrain from passing urine as long as possible.

II. Six to nine hours later, after specimens have been taken from the urethra for micro-

¹ This is prepared by the addition of bicarbonate of soda to the permanganate in the strength of 1 in 5000 immediately before use.

scopical examination and the patient has urinated, the irrigation is repeated as above. This is followed by the insertion of a 1 in 500 **acriflavine bougie** (acriflavine gr. $\frac{1}{12}$, theobroma oil grs. 35, glycerin q.s.—to make a bougie 4 ins. long). After insertion, this is worked gently towards the compressor muscle, "K-Y jelly"¹ being used as the lubricant. A small meatal dressing is retained by means of a fine strip of warmed adhesive plaster. The time for the insertion of the medicated bougie is last thing at night whilst the patient is in bed. The penis is maintained in the upright position with a loose collar of cotton-wool, and the patient is encouraged to retain the bougie as long as possible by refraining from passing urine. The intake of fluids, therefore, should be rigidly restricted during the first twelve hours of the intensive treatment. A **suppository** containing **extract of belladonna** gr. $1\frac{1}{2}$ and **morphine hydrochlor.** gr. $\frac{1}{4}$ is administered for the first three nights. If the rectum be loaded with faeces an *enema* should be given first. A morning *saline purge* is supplemented with *pure liquid paraffin* $\frac{1}{2}$ to 1 oz. thrice daily to ensure a free action of the bowels. It is extremely important to ensure a minimum of mechanical disturbance to the prostate during defaecation. The above measures, together with the action of the atropine contained in the belladonna suppository, will lessen the incidence of prostatitis, vesiculitis and epididymo-orchitis.

A dose of 5000 mill. **detoxicated polyvalent gonococcal vaccine** is given after the first treatment.

Second day.—The cargentos and the medicated bougies are discontinued. The patient is kept in bed and three irrigations of permanganate 1 in 3000 are given in the same manner as on the first day, but at 9 A.M., 3 P.M. and 9 P.M. respectively. During this day the patient is ordered to drink very copiously of plain or barley water (taking at least a gallon and a half in the twenty-four hours) to ensure hourly urination during the day, and two- to three-hourly at night.

Diet.—Boiled fish and milk puddings.

He is also given a six-hourly dose of the alkaline mixture mentioned on p. 393.

Third day.—The same treatment as on the second day.

Fourth day.—If the morning specimens from the urethra and centrifuged urine do *not* show the presence of gonococci, a morning and evening urethro-vesical irrigation of 1 in 3000 permanganate is given. The patient is still kept in bed under the same régime of medicines and dietary. The morphine is omitted from the suppository, but the belladonna continued.

5000 mill. detoxicated polyvalent vaccine administered.

Fifth, Sixth, and Seventh days.—Patient is allowed up, and the scrotum is supported in a well-fitting suspensory bandage.

Treatment as on the fourth day in the absence of gonococci in the morning specimens, excepting that the vaccine is withheld until the tenth day.

For the second week the patient is kept under daily observation, and at each single daily attendance he receives an urethro-vesical irrigation of 1 in 3000 permanganate. The suppositories are discontinued, but the medicine and dietary adhered to.

Specimens are examined at the middle and at the end of this week.

If all is well he discontinues all treatment at the end of the fortnight, and is told to report in a week's time for urethroscopic examination, from the result of which further attendances are decided upon.

Should gonococci be present in the morning specimens on the fourth day or subsequently, routine treatment is commenced, and the attempt to abort the infection is considered to have failed. Thus no harm has been done, and there is an excellent chance of shortening the attack very appreciably by the subsequent treatment.²

¹ K-Y Jelly manufactured by Johnson & Johnson, New Brunswick, U.S.A.

² It happens frequently that the schedule is unavoidably interrupted by the personal exigencies of the patient at a somewhat critical stage of the abortive treatment. In order to meet this contingency, Dr. Allport has devised a portable irrigation apparatus to be used by the patient himself. The apparatus is made of rubber, and is very compact and easily sterilised. (See Fig. 20 at end of this chapter.) It must be understood, of course, that this apparatus is only recommended to intelligent patients, who previously have been instructed in its use.

The writer has obtained considerable success with the above method, but, as pointed out, its employment in his hands has been confined almost entirely to private cases, and the great majority have been kept in bed for the initial five to seven days. Again, the cases have been carefully selected. Some will criticise it as being too "mild," but the writer now has ample proof that it is sufficient to abort the infection if commenced at a stage in the attack when an attempt is justified. Moreover, he does not feel in cases

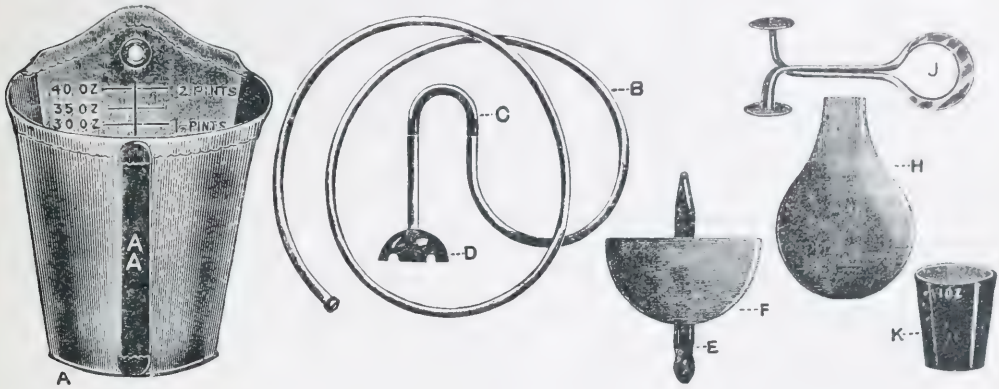


FIG. 20.—The St. Paul's Hospital Douching and Irrigating Apparatus, devised by Dr. Alfred Allport.

This douche has been specially devised and recommended at St. Paul's Hospital, London, and is easily sterilised by immersion in boiling water. The whole outfit occupies very little space, and by removing the vulcanite stay (AA) can be folded into a small compass, which renders it inconspicuous and is most convenient for travelling. The apparatus consists of the following parts:—

A—Graduated indiarubber container for the fluid to be used for douching.

AA—Vulcanite stay to be fitted into the slots in front of the container to keep it rigid. Unless it is for convenience when travelling, do not remove the stay, which supports the rubber part and keeps it in better condition.

B—Indiarubber tube to which is fitted vulcanite elbow (C) and metal sinker (D). The tubing should be adjusted over the elbow so that the sinker does not quite touch the bottom of the container.

E—Vulcanite urethral pipe. This is made in vulcanite to prevent breakage, but can be supplied in glass if preferred.

F—Rubber shield for backflow, to be used with pipe (E).

H—Pear-shaped rubber suction bulb for drawing the fluid through the tube to start the flow. It can also be used as a syringe by fitting on to either the urethral or vaginal pipes.

J—Spring clip to be fitted at the end of the tubing near to the vulcanite pipe to control the flow.

K—Vulcanite measure, capacity one ounce. This is made in vulcanite to prevent breakage, but can be supplied in glass if preferred.

DIRECTIONS FOR USE.

The container should be thoroughly cleansed with water almost at boiling point, and the tubing sterilised by running hot water through it immediately before and after use.

Fill the container (A) with the desired amount of hot water, to which add the quantity of solution according to the doctor's instructions. Place the sinker (D) in the container with the elbow (C) resting on the edge, so that the tubing (B) suspends without kinking. At the end of the tube fit vulcanite nozzle (E) with rubber shield (F) and adjust the spring clip (J), which controls the flow. Compress the rubber bulb (H) and fit to the end of the vulcanite nozzle, then release it so that the suction will start the siphon, when the douche is ready for use.

where it has failed that more drastic measures would have succeeded. Certain it is that they would have occasioned irritation resulting in mechanical damage.

If the attempt fails to abort the disease no damage will be caused such as might be calculated to prejudice the chance of an early cure ultimately. There are many opponents to the employment of urethro-vesical irrigation in the early stages, but with experience in attaining an extreme degree of gentleness in its administration, one will meet with none of those possible disadvantages which have been suggested. On the

contrary, there is much clinical evidence to support the assertion that potassium permanganate renders the mucous membrane unfavourable to the spread of the gonococcus.

In view of the fact that potassium permanganate in a dilution of 1 in 10,000 rapidly kills the gonococcus it is hard to conceive how one is in danger of "carrying the infection back" when employing a solution of 1 in 2000. Moreover, this is only permitted to enter the posterior urethra after the anterior portion has been thoroughly irrigated. With the above method one is able to merge gradually into routine schemes of treatment without any enforced rest under antiphlogistic measures. If we refer again to Macky's paper on the evils resulting from the abortive treatment of gonorrhœa, we find that in comparing the sequelæ resulting from various methods, he makes the following statements with regard to those who had been treated by irrigations with potassium permanganate: "Subsequent urethroscopic examination discloses little beyond the common mild littritis, and there is no mechanical damage to the urethra. . . . It is safe, and can be used with advantage at a stage when rapid-disinfection methods are too late."

Future Progress of Abortive Treatment.—It is possible that the next advance will be made in the discovery of a local disinfectant possessing the following properties to a higher degree than any yet at our disposal:—

1. The drug must be a powerful gonococcicide in weak solutions.
2. It must be well tolerated locally, and non-toxic.
3. It should not coagulate albumin.
4. It should possess the power of deep penetration into tissue, and a sustained bactericidal action.
5. It should be readily soluble in water, stable, and not decomposed by light and heat.
6. It should not be rendered inert by urine or soluble chlorides.
7. It should be hygroscopic rather than astringent in its action when used in concentrated solutions.
8. Finally, it should be cheap, odourless, and easily procurable.

The chief advances from a sociological point of view must necessarily evolve from any educational propaganda which is successful in stimulating patients to report at such an early stage of the infection that abortive treatment is rendered a hundred-per-cent certainty.

Efforts in the above two directions will be more likely to achieve success than will the elaboration of further complicated techniques in the abortive treatment of gonorrhœa.

C. H. M.

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PART VI

THE CLINICAL MANIFESTATIONS AND THE PRACTICAL MODERN TREATMENT OF GONORRHOEA

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CHAPTER XXXVIII

ACUTE GONORRHOEA

INCUBATION PERIOD: COURSE; SYMPTOMS AND SIGNS; PRIMARY EXAMINATION AND DIAGNOSIS; THE GLASS TESTS; TREATMENT; HYGIENIC AND DIETETIC RULES; MEDICAL TREATMENT; LOCAL TREATMENT; ABORTIVE TREATMENT—ACUTE ANTERIOR URETHRITIS OF OVER TWELVE HOURS' DURATION: ANTERIOR IRRIGATION; POSTERIOR IRRIGATION—ANTISEPTICS—ACUTE URETHRITIS, ANTERIOR AND POSTERIOR: SYMPTOMS AND DIAGNOSIS; TREATMENT OF ACUTE POSTERIOR URETHRITIS; VACCINE THERAPY IN ACUTE URETHRITIS

Incubation Period.—Like all diseases due to micro-organismal infection, gonorrhoea shows remarkable variations in the period which elapses between the actual infection and the onset of its primary symptoms. Most authorities state that in three to seven days the infection should have manifested itself, but one finds quite an appreciable number of cases in which the symptoms of infection do not appear for three weeks, and in some cases for even longer periods. The virulence of the organism and the resistance of the patient are the factors which influence the time of appearance, and if the former is excessive and the latter low, symptoms may appear as early as twelve hours after infection. Certain conditions predispose to infection, the chief among them being alcoholism, ill-health, phimosis and hypospadias.

Course.—Once the gonococcus is implanted in the meatus it rapidly proliferates, and spreads either backwards along the surface of the mucous membrane of the urethra, or along the ducts of the glands of Littre and between the layers of the columnar epithelial cells lining the urethra. On the method and extent of this spread depends, to a large extent, the success or otherwise of early abortive treatment. In a considerable number of cases the infection spreads in both directions, and quickly involves the whole surface of the urethra and the sub-epithelial tissues in addition.

Symptoms and Signs.—The first symptom complained of is slight irritation at the point of the penis, usually felt after passing water, and this irritation increases until it becomes a distinctly scalding sensation both during and after the act.

Shortly after this the lips of the meatus become moist, inflamed, and everted, and the moisture quickly gives way to the muco-purulent discharge, which manifests itself usually within twelve to twenty-four hours of the initial symptoms.

It is at this early stage that abortive treatment is of value, and that one can with hope of success try to abort the infection. If the condition is allowed to go on untreated at this stage, as in the majority of cases, or is self-treated by the patient with many of the familiar remedies, the organism rapidly proliferates, and extends backwards or penetrates deeply between the tissues. A temperature reaction is soon set up, varying from 99° to 100° F. and may persist for twenty-four to forty-eight hours. The discharge becomes purulent, and is accompanied by pain, swelling of the infected part, redness of the meatus, and at times frequency of micturition.

Primary Examination and Diagnosis.—After ascertaining the probable date of the infection and of the onset of symptoms, inquiry should be made as to previous infections, their date and duration. The patient is then questioned as to pain, its severity and site, and as to frequency of micturition. The patient should be stripped, so that the body from the shoulders to the calves can be examined; the prepuce is then retracted and the amount and character of the discharge noted. The prepuce is cleansed on both its surfaces with spirit. vin. meth.; similarly too the glans penis and the lips of the meatus. A sterile platinum loop is introduced between the separated lips of the meatus for from $\frac{1}{2}$ to $\frac{3}{4}$ of an inch, and some of the secretion obtained and transferred to a clean slide, over which it is thinly spread and fixed by passing through a flame. The film taken is then stained according to the methods detailed in Chapter III. One cannot too strongly deprecate the habit of not inspecting, or of only cursorily looking at, the infected organ. A thoroughly conducted examination at the first sitting often reveals evidence not only of a gonococcal infection, but also of a present or past attack of syphilis, either of which requires immediate attention. This is especially so in patients who have shown a long incubation period, and in whom the existence of a meatal chancre or a sub-preputial sore, with balano-posthitis as the cause of the discharge, is always a possibility. The epididymis and the vas deferens are next palpated and their condition on both sides noted. Cowper's glands, the prostate and vesicles are in turn examined by rectal palpation. This should be done gently, and affords valuable information as to the extent of the present attack, and as to the condition left by a previous attack. While doing so any pathological changes round the anus or on the skin of the back and of the legs are noted. The inguinal glands are examined as to size and consistence, and any pathological changes on the skin of the trunk or extremities are noted. Gonococcal infection in a large number of cases gives rise to a slight degree of adenitis, which disappears quickly with treatment, and is not of the painless indolent type associated with syphilitic infection.

Finally, the urine is examined, and while in the acute case seen early, the two-glass test gives valuable information when taken in conjunction with clinical signs. In the case seen later in the course of the disease, and in the more chronic case, this test is of little value, and does not negative the presence of a lesion of the prostate or of the posterior urethra, even if the contents of the second glass show no pathological changes. In such cases it is advisable to perform the three-glass test.

Two-Glass Test.—The prepuce, glans penis and meatus having been cleansed, the patient passes about six ounces of urine into a conical glass No. 1, and the rest of his urine into glass No. 2. If the contents of the first glass are turbid, or if it contains shreds of pus or muco-pus, while those of the second glass are clear, anterior urethritis alone is diagnosed. If both glasses are turbid or show shreds the indications are that the posterior urethra also is involved.

Three-Glass Test.—After cleansing the prepuce, the glans and meatus, the anterior urethra is gently washed out with a weak solution (cold by preference) of boracic acid, sterile water or normal saline, and the washings are collected into a conical glass. The cold solution causes the compressor urethræ muscle to contract, and so prevents any of the fluid entering the posterior urethra. The washed-out material in glass No. 1 represents the contents of the anterior urethra. The patient is then instructed to pass about

6 to 8 oz. of urine into glass No. 2, and this represents the condition and contents of the posterior urethra. The remainder of his urine is passed into glass No. 3, which represents the contents and the condition of the bladder. From the anatomical structure of the genito-urinary organs, and because of the continuity of the urinary tract, both these tests are scientifically inaccurate, and are liable to error, but, taken in conjunction with clinical signs, they are of value both in diagnosis and prognosis, and give a rapid and easy means of roughly estimating the extent of the disease and the effect and progress of treatment.

The tests are of much more clinical value if they are carried out when the urine has been retained overnight in the bladder. If this is not possible they should be performed when the urine has been retained for at least four to six hours prior to examination. It must always be remembered that in certain cases, *e.g.* in an acutely inflamed condition of the prostate, the urine may at times show few, if any, pathological changes, while in other conditions, such as that of epididymitis, the pathological changes as seen in the urine may be so slight as to be out of all comparison with the severity of the clinical condition.

It is only thus by weighing up all the evidence, the nature and amount of the discharge, the condition of the urine in the test glasses, the presence of pain, frequency and other clinical data, and by a thorough microscopic examination of the purulent discharge, that an accurate diagnosis can be arrived at. It is here that the clinician and the pathologist must work together to enable one to exclude the occasional cases of urethritis simplex that are met with, and to determine whether the infection is a purely gonococcal one or is complicated by an infection due to other pathological organisms.

Treatment.—There is no absolute hard and fast method which can be made applicable to the treatment of a gonococcal infection. Every case should be considered as an entity, and while abiding by close general principles, the duration of the attack, the severity of it, and the ability of the patient himself to carry out his part of the treatment, will greatly determine the course to be followed.

Hygienic and Dietetic Rules.—In few microbic infections is the attention of a patient to these rules of more importance than during the first six or seven days of an acute attack of gonorrhœa. Rest in bed is advisable, and if this is not possible comparative rest and avoidance of all physical strain should be aimed at. Harrison has pointed out that the incidence of complications in military patients varied directly with the amount of exercise which they were having and the number of fatigues they were performing, and the author's experience in the treatment of civilian patients bears out this fact. Cycling or motor-cycling, riding on horseback, dancing and all forms of athletics are contra-indicated. Heavy manual labour and lifting of heavy weights are also injurious.

A light bland diet is advisable for the first week, and all condiments, sauces and highly spiced foods should be avoided. Bland fluids should be taken in large quantities. There is nothing more suitable than milk and barley water taken frequently, and to make it more palatable it may be flavoured with orange or lemon juice. Weak tea in moderate amount may be allowed. At the end of the first week, fish, fresh fruit and vegetables may with advantage be added to the diet, and when the discharge has lessened in amount a fairly generous diet is permissible in the shape of boiled beef or mutton, veal, chicken, etc.

Alcohol in any form must be rigidly avoided, not only during the attack but for some considerable time afterwards.

General and local cleanliness aids in eliminating the infective process and in preventing complications.

Hot hip baths help to ease the local pain, and tend to reduce the local congestion, and are a great aid to cleanliness. Particular warning should be given to patients to avoid contamination of their eyes by their hands, and the eyes of other people by careless use of towels. A small bag, attached with tapes round the abdomen, can be fixed so as to collect the discharge from the penis and prevent soiling of the clothing. The cotton wool contained in it should be frequently burned and replaced, and must never be allowed

to press against the meatus and so to obstruct drainage. More important from the point of view of drainage is the position of the penis, and a well-fitting suspensory bandage, with supporting flap for the penis, not only helps drainage but also keeps the parts rested and supported. Most of those on the market are bad, and only accentuate the difficulty of drainage by pressing against the penis at the peno-scrotal angle of the urethra. An efficient bandage not only supports the scrotal contents but also the penis, and keeps it rested either along the inguinal fold or perpendicularly on the abdominal wall. This assists direct drainage, and that it is of great importance is confirmed by subsequent urethroscopy. Lesions are often found in this situation in chronic cases, and are due to kinking of the urethra and accumulation of the discharge which has not been able to drain away naturally. Plugging of the meatus with cotton wool is also bad, and tends to set up a balanitis and a posterior urethritis; it is very often resorted to by patients to prevent staining of the clothing, but this is better attained by the use of a gonorrhœa bag with a small pad of cotton wool in the base of it, the bag being fixed loosely over the end of the penis without in any way pressing against the meatus. By this means, during the acute stage of the discharge, the clothing is protected without in any way preventing effective drainage.

Medicinal.—Attention to the bowels is essential, and an initial dose of calomel grains i. or ii., followed by half an ounce of magnesium or sodium sulphate the next morning, is of value in the initial stage.

Daily evacuation of the bowels should be obtained during the subsequent course of the disease, and helps to prevent the onset of complications.

For many years drugs, chiefly of the oleo-resin class, have been used in the treatment of gonorrhœa. They have no specific action on the infective process, and any slight value gained from them is more than counterbalanced by their tendency to upset the digestive organs. Their administration in some cases appreciably lessens the amount of discharge, or may even cause it temporarily to disappear; but the cure is not absolute, and the symptoms return on the slightest lapse from careful hygienic and dietetic rules, thus showing that there is still present some focus of infection. Complications are a common accompaniment of the recrudescence of the symptoms in cases so treated.

In the early stages large doses of alkaline diuretics are of value, due to the fact, which Thomson has mentioned, that alkalis are deleterious to the gonococcus, and to the fact that the urine, being rendered alkaline, helps to clear away more effectively the pus and muco-pus from the crypts and lacunæ of the urethra. Bicarbonates in combination with acetate or citrate of potash in doses of 20 to 30 grains thrice daily act very well.

Bromides, hyoscyamus and buchu act as sedatives, and when painful erections are frequent these drugs can be advantageously combined with the alkaline diuretics mentioned above. Monobromate of camphor in doses of 5 to 7 grains in cachet form is a very useful drug in relieving chordee and painful erections.

In the later stages of the disease, and more especially in cases with chronic involvement of the prostate and vesicles, and in cases which require instrumentation, urotropin grains v., or boracic acid grains x., t.d.s., are useful. When prescribing urotropin, small doses only, grains v. to grains vii., should be given, as otherwise irritation of the mucous membrane is apt to be set up. This drug acts better in an acid urine, to obtain which acid sodium phosphate grains xx., t.d.s., should be administered concurrently.

Local Treatment.—There is no subject on which there has been so much controversy as on the method of applying local treatment to a gonococcal process. The local treatment indicated depends largely on the stage and duration of the infective process, and in the very earliest stage it is possible successfully to abort the condition.

Abortive Treatment.—This method of treatment has very marked limitations, and is available only in the very limited number of cases who report early after infection.

It should only be entertained:

(a) When the discharge has not become grossly purulent, or if so has not been present for more than twelve to twenty-four hours.

(b) When the anterior urethra alone is involved.

(c) When the methods employed are such that they will not prejudice the success of any subsequent treatment should abortion of the disease fail.

The earlier it is adopted the more hope is there of success, and of the advocated methods many are objectionable in that the solutions used are not only so strongly bactericidal as to kill the gonococcus, but are at the same time potent enough to destroy the mucous membrane, and so transform the urethra into a fertile living culture medium for other organisms, which are present normally in the preputial sac.

Silver preparations are perhaps those most commonly used for abortive work, and of these argyrol or hegonon is to be preferred. The latter is preferable, in that it does not coagulate albumin, and in that it is slightly alkaline in reaction. Colloidal silver is also very effective for this purpose. It is not injurious to the urethral mucous membrane and does not cause pain or coagulate albumin, even when used undiluted.

The following is the technique to be adopted: The patient empties his bladder completely, and the glans and prepuce are well cleansed with methylated spirit or a solution of hydrarg. biniodide 1 in 2000. The anterior urethra only is washed out with about one pint of a 1 in 4000 solution of hegonon, and subsequently an injection of half a drachm to one drachm of a 1 in 8 solution is slowly instilled into the anterior urethra and retained there for 5 to 10 minutes, after which, if the anterior urethra is at all distended, a little of the solution is allowed to escape. The meatal orifice is then carefully dried with sterile gauze, and cotton wool is placed over the meatus and sealed on by collodion in successive layers to prevent the silver solution from escaping. This done, the patient is instructed not to attempt to pass water, if possible, for four or five hours. This treatment should be repeated twice in twenty-four hours for two days, and the discharge, if any is still present, should be examined for the presence of gonococci each morning. By this means, if the patient can hold his urine, the bactericidal solution remains for a long time in contact with the infected mucous membrane and kills any gonococci which may come to the surface. If at the end of forty-eight hours there is still a discharge and if gonococci are present in it, abortive methods must be suspended, and the patient put on ordinary routine methods of treatment. If after two days of intensive treatment gonococci are absent, and the discharge has very appreciably lessened, irrigation of the anterior urethra for three or four more days with a solution of hegonon 1 in 4000, or of weak permanganate of potash once daily, is usually sufficient to clear up the condition.

Permanganate of potash can also be used for abortive treatment in strengths of 1 in 4000 to 1 in 1000, but its action is rather more astringent than that of the silver preparations. Acriflavine 1 in 1000 to 1 in 500 acts well also, although its staining properties are against its ever becoming a popular remedy. The same remarks apply also to the more recent preparation mercurochrome-220.

In addition to this local abortive treatment the bowels and skin should be looked after, and hot hip baths given to relieve the pelvic congestion. The patient should at the same time conform to all the rules recognised as essential in any acute inflammatory process, and put the parts at rest as much as possible.

Acute Anterior Urethritis of over Twelve Hours' Duration.—The condition by this time has become frankly purulent, and the gonococcus in many cases has invaded the whole of the anterior urethra, and in others has penetrated to the subepithelial connective tissues, and to the glands and ducts opening into the urethral canal.

The question of whether treatment should be carried out by injecting with a syringe or by irrigation with gravity apparatus is a vexed one. Both methods are good and serve their purpose in the hands of a skilled operator, but it so often happens that the patient himself has to carry out the greater part of the treatment and the teaching of a patient how properly to use a syringe is more difficult than the teaching of the use of the gravity apparatus. In view of this, if the patient is doing part of the treatment himself, it is always preferable to begin teaching him irrigation by gravity by Janet's

method, and to instruct him not to raise the vessel containing the solution to a height of more than $2\frac{1}{2}$ to 3 feet above the pelvis. The amount of pressure thus brought to bear on the compressor urethra muscle is never great enough to force the irrigating fluid past it, and the patient's left hand is free to control and assist the compressor muscle. In an infection confined to the anterior urethra it is better to wash out the anterior urethra only, but if there is any symptom or sign of infection of the posterior urethra the patient should be taught how to get the antiseptic fluid into the posterior urethra and bladder without excessive pressure or force. The patient may be instructed how to achieve this, or the surgeon himself may carry out the operation at each sitting.

Anterior Irrigation.—If a syringe is used it should be all glass in type with glass piston, and have a capacity of not more than 10 c.c. The point should be blunt and similar to that of a Janet glass nozzle.

If the gravity method is used the apparatus required is as follows :—

A vessel of one to two pint capacity, a metal sinker fixed to one end of 6 feet of rubber tubing, and close to it a vulcanite elbow, a blunt glass nozzle attached to the distal end, and an automatic clip on the tubing between. The equipment must be kept scrupulously clean. A waterproof apron $2' \times 2'$ with a central aperture for the penis is useful in keeping the patient's clothing dry, and makes the operation a more cleanly one. The vessel containing the irrigating fluid at a temperature of 104° to 106° (Fahr.) is placed on a shelf or hung up $2\frac{1}{2}$ to 3 feet above the patient's pelvis, whether he is standing, sitting or lying. The metal sinker at the proximal end of the tubing is placed in the irrigating fluid, and the fluid caused to flow along the tube by milking it and so inducing siphonage. The glans penis and prepuce are then cleansed with methylated spirit or a solution of 1 in 2000 biniodide of mercury. The left hand holds the penis between the thumb and forefinger, and with the right hand the nozzle is held lightly against the meatus. The clip is released, air bubbles are evacuated, and the flow is controlled by means of the forefinger placed immediately behind the nozzle. The anterior portion of the urethra is first washed out by allowing the solution to flow into the urethra without distending it; the nozzle is removed and the meatal opening held by the left finger and thumb for a minute or so, and the fluid then allowed to escape. This process is repeated ten to twelve times or until the antiseptic is returned clear. If the height of the irrigator is not above three feet the force will not be excessive, and the compressor urethra muscle will prevent any fluid passing into the posterior urethra. Half a pint of fluid is usually sufficient for washing out and thoroughly cleansing the anterior urethra.

Posterior Irrigation.—If the posterior urethra is infected and it is desired to get the antiseptic solution to pass into the bladder, the patient should first wash out the anterior urethra as above. He should then commence filling up the front part of the urethra, and as it is distending, strain slightly, as if in the act of passing urine, and immediately afterwards draw a deep breath to relax his muscles. If the nozzle is now firmly held against the meatus the fluid will automatically pass in through the relaxed compressor urethra muscle and thence without difficulty into the bladder. When the bladder begins to feel tense, the nozzle is removed from the meatus and the patient expels the antiseptic as in passing urine. Force should never be used in any part of the procedure, and is not necessary to overcome the contraction of the compressor muscle. In cases with a sensitive urethra, where difficulty is experienced in intra-vesical irrigation, the patient should be placed in the recumbent position, when the spasm of the muscle will be found to be much less in evidence. In cases of extreme difficulty a solution of alypin 2 per cent, or of novocain $2\frac{1}{2}$ per cent, applied to the urethra as an instillation, will overcome the spasm, and enable the irrigation to be satisfactorily accomplished. The bladder should be washed out at least twice by this method at each sitting, and the amount of antiseptic solution required for the complete operation is usually about two pints.

Antiseptics.—Local antiseptic treatment has for over a century been the chief method of dealing with gonococcal infection, and every one who has worked at genito-urinary

surgery must have been struck by the constantly changing views of clinicians on the question of which is the best antiseptic to exhibit in the acute stage of the disease, and what strength of it to use in each type of case.

The ideal antiseptic must be—

- (a) Toxic to the gonococcus ;
- (b) Non-irritating to the mucous membrane of the urethra ;
- (c) Able to penetrate living tissue.

There is not at present any antiseptic which will fulfil these three postulates. A great many fulfil the first, very few in the strengths commonly used the second, and practically none known the third. Of those commonly in use potassium and zinc permanganate and the silver salts are best known. Experimental work in the laboratory with acriflavine, and later still with mercurochrome-220, have held out hope of the discovery of an ideal antiseptic for use in urethral work, but the results *in vivo* have not been any more satisfactory than with previously tried preparations.

Those at present in use may be divided into the following main groups :—

- (1) Permanganates of potash and zinc.
- (2) Silver preparations, *e.g.* argyrol, protargol, hegonon, albargin, etc.
- (3) Flavine compounds, *e.g.* pro-flavine and acriflavine.
- (4) Mercurial salts, *e.g.* corrosive sublimate, biniodide of mercury and oxycyanide of mercury.
- (5) Astringent salts, *e.g.* zinc sulphate, alum sulphate, copper sulphate and zinc sulphocarbolate.

Eusol, picric acid, chloramine-T and many others have been tried, but with none of them have consistently good results been obtained.

While some of the continental schools favour the silver group of salts there is a general tendency in this country to adhere to the permanganate series as the most useful all-round antiseptics for urethral work, and especially so in the earlier stages of the infective process. Very rarely do they irritate, a feature which is often found on using many of the other groups. They can be used in sufficiently strong concentrations to destroy the gonococcus without injuring the mucous membrane, and they are to some extent astringent and anæsthetic in their action.

In an ordinary acute attack the strength of the permanganates to begin with should not be greater than 1 in 8000, and the action of these salts can be enhanced by rendering them alkaline immediately before use. The best method of doing so is by the addition of sodium carbonate in a strength of 1 in 5000. The addition of this to the permanganate should be made just prior to its use, and helps to dissolve the mucus and pus, and so to establish better drainage, while the alkalinity of the solution increases the toxicity of the antiseptic to the gonococcus. The alkaline salt is not irritating to the tissues if used in the strengths above mentioned, even in the earliest and most acute stages of an anterior urethritis.

As soon as the purulent or muco-purulent discharge has appreciably lessened it is better to reduce the alkalinity, or to change to a non-irritating drug such as chloramine-T 1 in 5000, or to a mercurial salt such as the oxycyanide 1 in 5000. Especially is this indicated if there is evidence of mixed infection. In the later stages one of the astringent zinc salts, such as the sulphate or the sulphocarbolate of zinc, may be used. These latter are stimulating in their action on the unhealthy mucous membrane. Care must be taken in all, and especially in the later stages not to overdo the use of antiseptics. When the muco-purulent stage has cleared up, irrigation if carried out too frequently does irretrievable harm, and is a potent factor in perpetuating the watery gleet so many patients suffer from. Chemical urethritis is a very common condition, and to prevent its occurrence it is absolutely essential at this stage to avoid irritation of the mucous membrane, and to leave a great deal of the healing process to nature, and if necessary to assist her by other methods which will be mentioned later.

If the gonococcus has penetrated between the columnar epithelial cells to the sub-epithelial tissues, or extended to the glands or gland ducts of Littre, there is no known antiseptic which will reach the infecting organism without damaging the mucous membrane, and irrigation in such cases can only be a means of temporarily cleansing the surface.

Acute Urethritis affecting Anterior and Posterior Urethra. The common cause of this condition is direct extension of the infective process from the anterior urethra. The factors which influence this spread are lack of treatment, too drastic treatment and badly applied irrigation or injections. Alcohol, heavy work, horse-riding, cycling, sexual excess, etc., are contributory factors. The infection may involve the whole urethral tract from the first, but more commonly several days elapse before the infective process extends to the posterior urethra.

Symptoms and Diagnosis.—The clinical evidences by which this spread of the infective process may be diagnosed are—

(1) The appearances of the urine in the glass tests, the second being usually, in the acute stage, hazy.

(2) The onset of frequency of micturition, and it may be of urgency of micturition.

(3) The feeling of pain at the end of the act of passing water, and occasionally the appearance of a drop of blood on completion of the act.

(4) The increase of painful erections.

Any or all of these signs and symptoms may be present, and rectal palpation of the prostate and vesicles will often give confirmatory evidence. If on palpation they are tender and inflamed, a condition present in the large majority of infections of the posterior urethra, both the prostate and vesicles are probably more or less affected by the gonococcal process, although not necessarily showing gross enlargement to the palpating finger.

Treatment of Acute Posterior Urethritis.—As in infections of the anterior urethra, an alkaline solution of potassium permanganate is the most useful antiseptic to employ, and there are few cases of posterior urethritis which do not bear it comfortably. If the inflammatory process is very acute, the most effective method of calming it down is to rest the patient in bed for twenty-four to forty-eight hours before exhibiting local antiseptic treatment. During this time the bowels should be emptied by calomel followed by a saline aperient, and hot hip baths should be given as often as conveniently possible. Alkaline diuretics, combined with hyoscyamus, should be freely administered, and plenty of demulcent drinks taken. If there are painful erections, bromides may be added to the prescription, or monobromate of camphor given. In hyperacute conditions, and in all cases in which on rectal palpation there is found to be gross involvement of the prostate and vesicles, washing out of the entire urethral tract should be delayed until the process has somewhat subsided, and the height of the irrigation apparatus when used later should not be more than three feet, and the strength of the antiseptic used comparatively weak. At all times it requires patience and perseverance to teach the patient how to wash out the whole urethral tract effectually, an essential in the treatment of this stage of the disease. If unnecessary force is used the infection may quite easily be carried along the vas deferens and an epididymitis set up. Atropine sulphate administered in the form of suppositories, in doses of grain $\frac{1}{2}$, of the sulphate combined with ext. opii grain $\frac{1}{4}$, or anti-febrin grains iii., if the pain is acute, may help to prevent the onset of this complication.

As the inflammatory process in the urethra subsides the heat of the antiseptic used should be gradually increased to 106° or 110° Fahr., and this is of more value than increasing its strength. In practically all such cases antiseptic treatment will not of itself cure the condition, because the antiseptic solution cannot penetrate the many side tracks, such as those leading to Littre's glands, or to the prostate and seminal vesicles, which are often infected.

To assist local methods of treatment in combating the infection in such cases, and especially in the large number of cases in which the subepithelial tissues are involved, the production of a true or an artificial immunity by the administration of a polyvalent

or autogenous vaccine is often invaluable. This therapy can be carried out at the same time as the local antiseptic treatment, and in the acute involvement of both the anterior and posterior urethra, will often lessen the duration of the inflammatory process, prevent complications being set up, and give a much greater certainty of actual cure. Either method used alone is unsatisfactory; in combination, excellent results are obtained.

Vaccine Therapy in Acute Urethritis.—It is well known that the tissues do not respond quickly to a gonococcal infection by producing antibodies. The more localised the lesion the more marked is this fact, and it is difficult in many cases to demonstrate the presence of this specific antibody in the blood serum before the second or third week of a gonococcal infection. Improvements in the technique of the complement-fixation test have enabled Thomson to show that it is produced in small quantity by the third day of the actual onset of symptoms in almost every case, but never at this early stage in sufficient quantity to cut short the purulent process. That this production of antibody can be stimulated and increased by carefully administered doses of a specific vaccine is well known, and in no acute infective process have better results been obtained in doing so than in acute urethral infections. There are comparatively few cases of spontaneous cure of acute gonorrhœa, and the early and careful administration of a good antigen, either autogenous or polyvalent, is of great assistance in cutting short the inflammatory process, in preventing its further extension, and in preventing the subsequent onset of the more serious complications which follow on acute gonorrhœa in both sexes. Just as the virulence of the infecting organism and the inherent resistance to infection of the patient vary, so do patients differ in the way their tissues respond to the administration of a specific vaccine. On this account it is always a wise precaution to start with a dose which will not set up too big a reaction, either local, focal or general, and to judge by the effect of this initial dose what intervals should elapse between doses, and whether an increased dose can with safety be given later. The clinical course of the case and the reactions resulting from the vaccine, especially the focal and general reactions, are the best guides to further dosage, and should at all times be preferred to any rule of thumb method of automatic increase of dosage at fixed intervals. The failures of vaccine therapy in gonococcal infections are more often due to the haphazard methods of exhibiting this mode of treatment than to the lack of efficiency of the vaccine. The local reaction at the site of administration is usually manifested by slight stiffness in the muscles only, but there may be swelling and redness; the focal reaction is seen in a temporary slight increase of the amount of purulent discharge, and the general reaction set up is evidenced by a rise of temperature varying from 1° to 2° Fahr. These reactions should be carefully observed, and if any or all of them are severe, it is an indication to decrease, or at any rate not to increase, the initial dosage. In all cases the acute focal and general reaction set up should be allowed to calm down before administering the succeeding dose. In general one may say that in gonorrhœa a good stock polyvalent vaccine is more useful than an autogenous one. Valuable time is lost in preparing the latter, and even when prepared it may not have so good antigenic properties as the polyvalent type, which can be prepared from known good antigenic strains. The more acute the gonococcal process the smaller the initial dose should be, and as a general rule ten to twenty millions is a good average dose to start with in an acute urethritis. The toxicity of the vaccine used is always a factor to be reckoned with, and Thomson, as described in Chapter XXXI., has been able to overcome this by eliminating the toxic elements of the organism. He has prepared a vaccine which, while still as potent antigenically, is very much less toxic, and can as a result be administered in very much larger doses without giving rise to large reactions, either local, focal or general. This great reduction in toxicity has enabled much larger doses to be given, and the increased antigenic power obtained by the larger dosage of the detoxicated vaccine is of extreme value in rapidly stimulating antibody output on the part of the tissues and cutting short the infective process. An initial administration of five thousand millions of detoxicated gonococcal vaccine will result

in less focal and general reaction than that set up by the administration of one hundred millions of the same strains of ordinary gonococcal vaccine. While this is so, the end results as seen clinically are even more striking, the detoxicated vaccine setting up an immunity more quickly, and enabling the patient more rapidly to overcome the infecting process. These clinical results can be confirmed by serological tests of the patient's blood serum, which show the progressive increase of antibody following on repeated doses of detoxicated vaccine. There is no doubt that the earlier the non-toxic vaccine is used the better are the results, and vaccines are of use even in those early cases where an attempt can be made to cut short the infection by abortive methods. The earliest and in some ways the most important sign of the success of a vaccine in gonorrhœa is the feeling of well-being which the patient is conscious of within a day or two of its first administration. In a condition which naturally gives rise to a certain amount of depression this action is valuable, and especially so in the patient who must in many cases continue at his occupation and cannot afford to lie up in bed or be admitted to a hospital for treatment.

Of the methods of administering the vaccine, intramuscular injection is preferable in the out-patient, and in the case of those who cannot lie up, in that it gives rise to much less local reaction, and is perhaps more rapid in its mode of action; subcutaneous administration gives a longer and more continuous immunity response, but causes rather more local stiffness and pain. Of the detoxicated vaccine an initial injection of one thousand to five thousand million organisms can usually be administered with safety in the large majority of cases, and the dose may be gradually increased at intervals of four to seven days according to the focal and general reactions. The average case of anterior or of posterior urethritis will clear up effectively with a total of six or seven injections of detoxicated vaccine given at intervals of five days over twenty-four to twenty-eight days, and a total of fifty to seventy thousand millions of gonococci is in most cases sufficient to immunise the patient, and, in conjunction with careful hygienic and local treatment, to rid him of his infection. If the case is under observation and treatment before the third day, two or three doses may suffice to cure the infection, but it is always advisable to continue the immunisation process although local antiseptic treatment is abandoned. By this means the patient's resistance is increased and a more lasting immunity conferred.

In cases so treated by large doses of detoxicated vaccine the output of antibody progressively increases as a result of successive doses. As indicated by the complement-fixation test it is, on the average, greatest about the fourth or fifth day after giving the vaccine, and it is on this account that this interval is chosen as the most suitable one to repeat the succeeding dose.

While the clinical picture and the serological one are the best guides as to the increase or otherwise of the dose in any given case, the following table of intervals and dosage may be found useful where large numbers are being treated and close personal observation of each case is difficult:

1st day	.	.	.	5,000 millions
5th "	.	.	.	6,000 "
9th "	.	.	.	7,500 "
13th "	.	.	.	10,000 "
17th "	.	.	.	10,000 "
21st "	.	.	.	15,000 "
28th "	.	.	.	20,000 "

When a polyvalent detoxicated vaccine made from good antigenic strains is carefully administered and repeated according to the reactions, and at the same time local antiseptic treatment is carried out, the average case will clear up both quickly and effectively. Both methods are essential; the action of the warm antiseptic is important in that it causes the blood serum to flow more freely to the inflamed surface of the urethral canal, and this antibody-laden serum exercises a curative effect on the infective process. The

earlier the blood serum is showing a preponderance of this antibody the more rapid the cure and the less likely the involvement of any of the deeper structures or any permanent damage to the urethral mucous membrane. In cases in which the infecting organism has penetrated further than the surface of the urethra, the administration of a vaccine is still more essential, as antiseptic therapy is limited in its effect on such cases, and treatment through the blood stream is the only certain method of getting at the organisms and of ensuring a permanent cure.

This applies still more potently to those cases of posterior urethritis in which there is inflammatory involvement of the prostatic ducts and of the prostate gland itself. These ducts easily become closed up by inflammatory deposit. On this account, in the declining stages of the inflammation the prostate and vesicles should be massaged to ensure drainage from them, and at the same time to improve the local circulation so that the antibody-laden serum may reach the infected areas. If this is done before the acute stage has subsided, gross general reactions are apt to result, and especially so if at the same time as the massage is given, a vaccine is administered. This is due to the fact that massage of the active focus of disease sets free into the circulation an auto-vaccine. It is thus advisable to avoid the simultaneous carrying out of these two methods of treatment at one sitting. Prostatic massage, however, should never be omitted as a routine part of the treatment. If it is not carefully carried out, a small closed-in focus of infective material in a non-vascular structure may remain dormant for days or weeks, and later on give rise to an acute exacerbation or may remain a fertile source of quiescent infection in a gonococcal carrier over a very long period.

CHAPTER XXXIX

SUBACUTE OR CHRONIC GONORRHOEA

CAUSES, SYMPTOMS, SIGNS AND DIAGNOSIS—GENERAL TREATMENT IN SUBACUTE STAGE.
LOCAL TREATMENT OF THE URETHRA — OPERATIVE TREATMENT — VACCINE THERAPY
IN SUBACUTE URETHRITIS

ANY case of gonococcal urethritis which has been under treatment for twenty-eight days and does not show signs of clearing up may safely be classed in the above category, and it is in such cases that the difficulty of treatment begins. When a case ceases to be subacute and becomes chronic is immaterial. The difference is simply a question of degree, and the treatment of both conditions must lie along the same lines. The first principle of treatment is to find out the reason why the symptoms are not clearing up. In such cases close clinical observation of the patient is required. The urethroscope is of great assistance, and, combined with pathological examination of the discharges, should be utilised to supplement one's knowledge of the clinical condition.

Causes.—The common causes of failure of an acute urethritis to clear up are :—

- (1) Infection of one or more of the glands of Littré, the ducts of which are also infected and may be blocked up.
- (2) Soft inflammatory infiltration of the urethral mucous membrane.
- (3) Infection of one or both of Cowper's glands.
- (4) Infection of the prostate and vesicles.
- (5) Chemical urethritis.
- (6) Lowered resistance of the patient.

Symptoms, Signs and Diagnosis.—While these will vary with the different causes, in general one may say that the main sign of delay in resolution is a persistence of the urethral discharge, either muco-purulent or watery in nature. Associated with this there are usually, but not necessarily, pus-threads present in the urine. The meatus appears sticky and its lips are adherent in the morning, and this may be the only sign present. Conditions such as a peri-urethral abscess, a lacunar abscess, Cowperitis and prostatic enlargement, etc., are often met with in the subacute stage, and will be described later in connection with the discussion of each lesion.

The accurate diagnosis of the existing lesion is only possible by a close clinical and pathological examination of the whole genital tract. One or more areas of infection in the same person, for example, a Littritis and a prostatitis, may coexist, and it is only by clinical methods such as careful examination of the urine, and careful palpation of the prostate and vesicles in combination with bacteriological methods to verify the cause of the inflammatory action, and operative measures, such as the use of the acorn-tipped bougie and other instruments, that the site of the subacute process may be with certainty located and effectively treated. Each or any combination of these conditions may occur in the subacute stage of the disease, and the diagnosis and treatment of each condition will be dealt with under the "Complications of Gonorrhœa."

General Treatment—Subacute Stage.—Careful dieting is not specially called for in this stage, and the aim should be rather to build up the general health of the patient, and to make certain that the skin, bowels and kidneys are acting well. Exercise in moderation may be taken, but all vigorous athletic pursuits are contra-indicated. Medicinal treatment is of little or no value.

Local Treatment of the Urethra.—In general this should be administered according to the clinical signs, and it is not necessary to irrigate the urethra at such frequent intervals as in the acute stage. In the case, for example, of a Littritis or of soft infiltration of the urethra, the local antiseptic used in the irrigation process acts much better subsequent to the opening up of the gland duct by the passage of a straight bougie, or subsequent to stretching of the infiltrated area by a Kollmann's dilator. Similarly in infections of the posterior urethra which have reached the subacute stage, intravesical lavage is more effective subsequent to massage of the prostate and vesicles. The value of local antiseptic treatment in all subacute conditions is limited from the antiseptic point of view unless one ensures that the antiseptic reaches the infected area, and it is in this stage that the action of the heat of the fluid used is important in that it increases the flow of blood serum to the part. It is not necessary to increase the strength of the antiseptic, and better results are often obtained by changing the antiseptic from week to week, thus preventing a tolerance being set up to any given drug. In general, albargin, oxycyanide of mercury and chloramine-T are the most useful antiseptics in this stage. Strong antiseptics are contra-indicated in that they irritate the mucous membrane and give rise to chemical urethritis, while they do not destroy organisms which they do not reach on account of their not being able to penetrate living tissue. A solution of 1 in 5000 of any of these antiseptics is generally potent enough to destroy the infecting agent.

Operative Treatment.—In subacute conditions this is called for very rarely, apart from the passage of a straight bougie or of a suction bougie in Littritis, or of the solid dilator or the expanding Kollmann's dilator in cases of infiltration. The use of these various instruments will be dealt with later. There are certain cases in which only one gland duct or so is involved, and in such the healing process may be hastened by topical applications through the urethroscope of silver nitrate 1 per cent, or tincture of iodine 2½ per cent. These single conditions are uncommon, and will be mentioned subsequently under urethroscopy.

Vaccine Therapy in Subacute Urethritis.—Even more so than in the acute condition vaccines are indicated in the subacute condition in combination with and to assist local treatment. The method of administering them is the same as indicated earlier, but the dosage may be appreciably increased in the subacute stage without producing gross reactions either local, focal or general. In treating a case of gonorrhœa by vaccines in the subacute stage it is essential to open up and vascularise the tissues, so that the blood may circulate freely through the infected area. This is specially indicated in cases of subacute prostatic and vesicular involvement, and the failure to do so accounts for a very considerable number of those cases which do not clear up with the administration of vaccines. It is essential to remember also that in this stage there is often an infection by other organisms than the gonococcus, and specific therapy is required in order to obtain the best results. Subacute cases will react quickly to vaccine treatment when an autogenous vaccine of the secondary organism or organisms present is given in addition to a gonococcal vaccine.

Successful treatment of chemical urethritis can be attained by the cessation of all local treatment, followed at a later date by the passage of bougies or a dilator to prevent subsequent narrowing of the urethral canal.

In these subacute conditions a good working knowledge of clinical pathology is a valuable asset to the person in charge of treatment. Periodical examination of the secretions, both urethral and prostatic, should be made by the clinician or by a competent bacteriologist, and close touch kept between the clinical and pathological worker. Such

co-operation will give more accurate diagnosis, will accelerate the cure and give a greater certainty of cure.

Cases are encountered occasionally where the resistance of the patient is so low that improvement proceeds very slowly in spite of all forms of treatment. In such cases complete cessation of local and vaccine treatment for eight to ten days, and during this time the administration of small doses of nuclein or allantoin, will often materially assist in building up the patient's resistance. These preparations act by stimulating a general leucocytosis, which aids materially the subsequent local and vaccine therapy.

CHAPTER XL

CHRONIC GONORRHOEA OR GLEET

CAUSE, SYMPTOMS AND DIAGNOSIS, TREATMENT. OLIVARY BOUGIES—STRAIGHT AND CURVED SOLID SOUNDS—THE URETHROSCOPE—SUCTION APPARATUS—THE MEATOTOME—INTRA-URETHRAL SYRINGES—GRADUATED MECHANICAL DILATORS

Cause.—This generic term is applied to all cases of urethritis in which there has been a pre-existing gonococcal infection of some part of the tract which has failed to clear up satisfactorily. It may be due to (1) lack of power on the part of the individual to overcome the infective process; (2) the persistence of an infective focus of low virulence, partly shut off from the circulation and from the urethral tract by fibrous tissue; (3) the damage done by the gonococcus to the tissues of the urethral tract; (4) a superadded mixed infection of the urethral tract, not necessarily gonococcal in nature; (5) over-treatment by antiseptics and by instruments.

Symptoms and Diagnosis.—When the urethral discharge is no longer copious and is only like glycerine or watery in nature, or when it intermits and the patient is free from discharge for days in succession, apart from some stickiness at the meatus in the morning, the condition is recognised as chronic gonorrhœa. In many cases by careful bacteriological examination of the secretions or by culture, one is able to demonstrate the gonococcus; in others, this is not possible, and other organisms are responsible for the persistence of the urethral discharge, however slight. The latter condition is not necessarily gonococcal, and should be called chronic urethritis. In cases in which there are no organisms present the condition is one of simple gleet. The diagnosis can only be made accurately by clinical observation of the local condition at the meatus and of the morning urine, by carefully palpating, as far as possible, the whole genito-urinary tract, including the prostate and seminal vesicles, supplemented by endoscopic examination. In addition to these methods, bacteriological and cultural examinations of the urethral and prostatic discharges are helpful in demonstrating the causal organism. In some cases the complement-fixation test may be of value in diagnosis. This condition of gleet has long been recognised as one of the most difficult with which the clinician has to deal, and is responsible for a great amount of chronic ill-health and neurasthenia. Many patients get depressed and begin to think themselves incurable, and drift from one medical man to another in search of a cure.

Treatment.—This is entirely dependent on accurate diagnosis of the cause of the condition. Lessened resistance on the part of the patient can be improved by the methods previously described and by careful administration of a good antigenic and specific vaccine. A closed-up focus of infection may be dealt with surgically by establishing drainage from it to the surface, and the various methods of attaining this will be dealt with under Littritis. Damage to the tissues by the gonococcus and other organisms is usually the result of a submucous infiltration, and calls for dilatation. Secondary infection reacts either to an autogenous vaccine or to a polyvalent detoxicated gonococcal

vaccine in combination with one prepared from the specific infecting organism. Over-treatment will cure itself in time if the condition be left alone.

Focal treatment by potent antiseptics is rarely of much use in any of the above conditions, and often does definite harm in inducing a chemical urethritis. In all these conditions the urethroscope is invaluable for purposes of diagnosis and for observation of the effect of treatment. Once a diagnosis is established the focus of infection, if there be any, can be satisfactorily cleared up by methods such as prostatic massage, by suction or by careful dilatation of the urethral canal, using either Kollmann's irrigating dilator or solid sounds of the Bénéqué type. In cases with lessened resistance a change of climate is often effective in that it improves the general health of the patient, while in certain of these cases sodium nucleinate, min. x. thrice daily, is of benefit in that it sets up a leucocytosis with a resultant increase in the antibody output of the tissues.

In many cases it is essential to combine various forms of treatment. If the diagnosis has been accurate, every case can in time be effectually cleared up by combining local and vaccine treatment.

In a chronic gonococcal process instrumental interference is often essential, not only for diagnosis, but also for effective treatment. The olivary bougie, straight and curved solid sounds, the urethroscope and suction apparatus, may all be used to establish an accurate diagnosis. In addition to these the meatotome, Guyon's or Ultzmann's syringe and Kollmann's dilators, both anterior and posterior, of the irrigating type are frequently required in the treatment of subacute and chronic complications.

Electrical apparatus, ionisation bougies, and the urethrotome have a more limited application and are rarely required.

Olivary bougies, with an acorn tip, are used to ascertain the position of the lesion in the urethra. The bulbous head of the bougie as it is passed along the urethra causes a sensation of pain to the patient when it comes against any inflamed part. It also imparts to the surgeon's fingers a sensation of resistance to the passage in and out of the instrument.

Care must be taken not to mistake for a pathological condition the slight resistance which is felt just as the instrument enters the membranous urethra, and again as it enters the bladder.

Straight and curved solid sounds may be used for the same purpose but are more frequently used in treatment, their purpose being to distend the urethra, to displace plugs of mucus and muco-pus from the openings of the gland-ducts, and to act as a mild irritant to stimulate the flow of blood to the urethral surface. Of those in use Wyndham Powell's or Canny Ryall's are suitable for treatment of the anterior urethra, Bénéqué's or Guyon's for that of the posterior urethra.

The urethroscope consists of a metal tube with an obturator to enable it to be introduced into the urethra, and with a lighting mechanism attached to it. There are two methods of illuminating the urethral surface, either first by reflecting an external light into the tube by mirrors, or secondly by a small lamp carried inside the tube to its distal end. Wyndham Powell represents the first type, and Cambell's, Wolff's, or Luys' the latter type of instrument.

For the anterior urethra the tube is straight, and the best sizes are 20, 22, and 24 Charrière scale. The instrument is about $5\frac{1}{2}$ to 6 inches long. For the posterior urethra the tube used is longer, $6\frac{3}{4}$ to 7 inches, and has a curved beak. The obturator in the posterior instrument reaches and fills up an opening on the convexity of the curve, and opposite this opening there is a fixed lamp inset into the tube for illuminating purposes. Wossidlo's and Ringliebs' instruments are two of the best known, and the calibre of the tube is usually 22 or 24 Charrière scale.

At the outer and proximal part of both anterior and posterior instruments there is attached a system of lenses to magnify the endoscopic picture, and also at the side of the endoscopic tube in some types an opening for the introduction of air to distend the

urethra during the examination. This air distension, controlled by a stop-cock at the entrance to the tube, gives a larger field, and enables operative measures to be carried out more effectively and easily through the tube.

Apart from its value in the diagnosis of Littritis, infiltrations, peri-urethral abscesses and stricture, the urethroscope enables operative measures by such instruments as the cautery and the curette to be carried out under good illumination, while air distension steadies the part, shows the dilatability and resilience of the canal, magnifies the field, and allows of topical applications to the wall of the canal.

Suction Apparatus.—Mills' instruments consist of a framework of four blades, which keep the urethral walls apart, a conical point and a central lumen, the proximal end of the instrument having a narrow tube to which may be attached a rubber suction pump or a pump with manometer. By means of such simple apparatus the retained secretion and plugs from the gland ducts of Littré and other side tracks may be aspirated and examined microscopically for gonococci, while at the same time drainage is satisfactorily established without damaging the urethral surface, and Bier's congestion is applied to the suctioned surface. (See Fig. 21.)

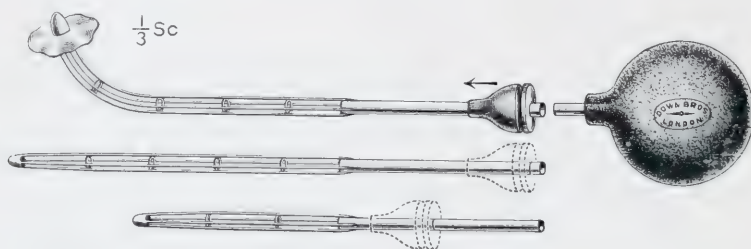


FIG. 21.—Mills' suction bougies for the anterior and posterior urethra.

Cambell's apparatus is rather more complicated, but acts in the same manner.

The meatotome is at times necessary to enable instruments to be passed through the meatus, which is the narrowest part of the urethral canal. Meatal dilators may also be used to examine the first inch or so of the urethra.

Intra-urethral syringes of the Guyon or Ultzmann type are used to apply instillations of caustic or antiseptic solutions to any part of the urethral canal, especially to the deep urethra. These same applications may be applied through the urethroscopic tube by means of the Geraghty syringe, and this method is preferable, as there is then the certainty that the application is limited to the diseased part and reaches it. Similarly under a good light the electric cautery or fused silver nitrate on a probe may be used to cauterise any area through the urethroscopic tube.

Graduated Mechanical Dilators.—The best known are those of Kollmann. The straight instrument is used in the anterior urethra, the curved type in the posterior. Both types have provision made for irrigation of the urethra during the process of dilatation. These instruments are of great value in dilating the canal and in opening up the mouths of the gland ducts. By their dilatation they break down any newly formed fibrous tissue and infiltrates, and cause the resolution of early stricture formation. They also stimulate the rapidity of the healing process in the chronically inflamed urethra, and are helpful in finding out areas of latent infectivity.

Hot-water bougies and electro-medical apparatus may be used, but the results have not been such as to establish their general utility in the treatment of chronic gonorrhoea.

CHAPTER XLI

THE LOCAL COMPLICATIONS OF GONORRŒA

GLANS AND PREPUCE ; BALANITIS, PARAPHIMOSIS, TREATMENT. INTRA-MEATAL ABSCESS, LITTRITIS, TREATMENT. PERI-URETHRAL ABSCESS, DIAGNOSIS, TREATMENT. SOFT INFILTRATION OF THE URETHRAL MUCOUS MEMBRANE, DIAGNOSIS, TREATMENT. COWPERITIS, SYMPTOMS, DIAGNOSIS, COURSE AND TREATMENT. INFECTION OF PARA-URETHRAL CANALS. PROSTATITIS. PROSTATIC ABSCESS, TREATMENT. ACUTE PROSTATITIS, SYMPTOMS AND DIAGNOSIS. SUBACUTE PROSTATITIS. TREATMENT OF ACUTE AND SUBACUTE PROSTATITIS. PROSTATIC MASSAGE. CHRONIC PROSTATITIS, SYMPTOMS, DIAGNOSIS, TREATMENT. SPERMATO-CYSTITIS, SYMPTOMS, DIAGNOSIS, TREATMENT. DEFERENTITIS. EPIDIDYMITIS, SYMPTOMS, DIAGNOSIS, TREATMENT. CYSTITIS, SYMPTOMS, DIAGNOSIS, TREATMENT. URETERITIS. PYELITIS AND PYELO-NEPHRITIS, SYMPTOMS, DIAGNOSIS, TREATMENT. PROCTITIS, SYMPTOMS, DIAGNOSIS, TREATMENT. ADENITIS AND LYMPHANGITIS

Glans and Prepuce.—Both the glans and the inner surface of the preputial sac may be affected in gonococcal lesions. A pure gonococcal infection is uncommon, as this region is the natural habitat of numerous saprophytic organisms, which take on increased virulence subsequent to the surface being damaged by the gonococcus.

Balanitis.—In nearly all such cases the prepuce is long and has a narrow orifice, rendering it difficult for the patient to cleanse the parts. The inflammation set up by the infecting organism causes a serous and then a sero-purulent discharge. This does not drain away easily, and the adjacent surfaces of the glans and prepuce become red, angry, and bathed in pus. The resultant swelling renders the condition worse, and if not treated, necrosis and sloughing of the tissues may follow.

Paraphimosis.—In other cases in which the prepuce is not so long the swelling set up by the inflammatory reaction may result in the prepuce slipping back and forming a tight ring behind the coronal sulcus. Both conditions are painful and require prompt treatment.

Treatment.—The paraphimotic condition is usually easy to reduce if pressure is applied carefully and continuously by an elastic bandage to the glans penis to reduce the swelling on the distal side of the constricting band. Subsequent to this the retracted prepuce can be pulled forward with the fingers, while the glans is pressed back simultaneously by the thumbs. If not relieved, ulceration and sloughing takes place. Very rarely is it necessary to incise the constricting band, or employ other operative measures.

Phimosis complicated by balano-posthitis is in uncomplicated cases an easy condition to clear up. Rest and support of the penis by a proper suspensory bandage ease the pain. Local applications of magnesium sulphate in a strength of 2½ to 5 per cent, and applied as a foment, are of great assistance in reducing the œdema. By this means, and by syringing through the narrowed orifice with a mild antiseptic, it is possible quickly to clear up the septic condition and reduce the painful swelling.

In a considerable number of cases it is advisable to have recourse to circumcision, especially as the phimotic condition renders the local treatment of an infected urethra difficult. The fact that the area is septic does not contra-indicate operative measures, and nearly all cases do well if the prepuce is left sufficiently long to allow for the retraction that takes place once the oedema has subsided. Local anaesthesia is, in most cases, quite satisfactory for carrying out this operation. In cases in which, from the clinical signs and the history, one has reason to suspect a sore on the coronal sulcus or on the under surface of the prepuce, it is preferable to remove a triangular wedge of tissue from the dorsum of the prepuce, the apex of the wedge extending up to or even beyond the sulcus. This gives excellent access to the local lesion, and in the long run a good cosmetic result. Very few stitches are required to approximate the edges, and this method of exposing the inflamed sub-preputial surface is preferable to the simple dorsal slit, which leaves a large apron-like piece of tissue on the under surface of the prepuce. Subsequent to circumcision or other operative measures hot antiseptic baths and dressings of tinct. benzoini co. or of sulphur powder are the most effective applications.

Intra-meatal Abscess.—This is quite a common condition, and is usually due to saprophytic organisms which have become pathogenic in one or more of the small blind para-urethral ducts which are present just inside the meatus.

Diagnosis.—When it occurs the lips of the meatus are constantly gummed together in the morning by muco-purulent secretion and there is a tickling sensation at the point of the penis. The condition is very liable to recur.

Treatment.—The quickest and most effective method of clearing up such an abscess is the application of the electric cautery to destroy the infected duct. Such a condition must always be differentiated from a meatal chancre, but this is not difficult, as the latter is more indurated, less angry, and the spironema pallidum can be demonstrated in the serum expressed from it.

Littritis.—This condition involves both the gland-duct and the gland itself. It varies in severity, and is responsible for the larger number of cases of anterior urethritis which persist for any length of time. It is the commonest of all the complications of urethritis and is a fertile source of chronicity.

Diagnosis.—The urine passed in the first test glass is turbid and shows gross urethral pus-threads, but may occasionally be clear. This discrepancy is due to the anatomical structure of the gland-ducts. Their openings tend to become closed up with plugs of mucus or muco-pus, and the resulting closed-in pus-sac may empty itself periodically with intermissions. When the ducts are closed up the urine is usually clear. The simplest means of diagnosing the condition is the passage of an acorn-tipped bougie (bougie à boule), the bulbous end of which enables the observer to locate the affected area. The passage of a metal bougie into the anterior urethra, and subsequent palpation on it of the whole anterior urethra, also gives valuable information, especially if there is more than one duct involved. The urethroscope is perhaps of greatest assistance, in that it enables one to see with the naked eye the inflamed and reddened openings of Littré's gland-ducts, and to observe pus or muco-pus oozing from them.

Treatment.—In treating this condition antiseptic therapy is very limited in value. There is no certainty of the antiseptic penetrating to the infected gland. Topical applications through the urethroscope are also limited in their curative effect. Those most commonly used for this purpose are fused silver nitrate and tincture of iodine 2½ per cent, but there is no certainty that the medicament, when brought into contact with the opening of the duct, will penetrate the gland-duct, which is tortuous and runs at an angle to the direction of the applying probe. The passage of a solid bougie and subsequent massage of the urethra on it is helpful, in that it enables the duct to be emptied and drainage established. This end, however, can be more effectively accomplished by the use of a simple suction bougie, such as that of Mills. This instrument does not destroy or crush the tissues, while it opens up the gland-ducts and at the same time, as a result

of Bier's congestion, stimulates the urethral surface to healthy action. If only one gland and its duct is infected, the application through the endoscope of tinct. iodi deeply into it, and subsequent irrigation of the canal are often effective. Better results, however, in the case of a single infected follicle, are obtained by the use of the electric cautery applied through the endoscope to destroy the whole of the infected gland.

In all cases of Littritis, with a view to preventing stricture formation at a later date a series of graduated bougies or a Kollmann's dilator should be used either during or immediately after treatment. This gradual dilatation of the urethra before discharging the patient as cured is in addition a valuable test of cure in such cases.

Peri-urethral Abscess.—*Symptoms.*—In a certain number of cases of Littritis, especially in the acute stage of the infection, the gland-duct becomes blocked and the gland quickly enlarges. The suppurating process extends into the tissues surrounding the gland and becomes a peri-urethral abscess. The pus-sac may bulge into the tissues of the corpus spongiosum penis or urethræ, and is then distinctly palpable on the outer surface of the body of the penis. The common sites of a peri-urethral abscess are the bulb and the fossa navicularis, and in the latter position the abscess simulates a meatal or intra-urethral chancre. A peri-urethral abscess should never be allowed to burst outwards through the skin, and should not be incised externally. If untreated it may burst internally into the lumen of the urethra or outwards through the skin. If the latter occurs a very intractable urinary fistula may remain.

Diagnosis.—The diagnosis is usually easy. There is pain on passing water, the penis becomes swollen and often œdematous, and the abscess, which may reach the size of a cherry, is palpable in the corpus spongiosum. The urethral discharge is increased temporarily in amount, and the urine in the first test glass is always hazy.

Treatment.—The anterior urethra should be washed out with a mild antiseptic, e.g. $\frac{1}{2}$ per cent boracic acid. The mucous surface is then anæsthetised with novocain $2\frac{1}{2}$ per cent and a urethroscopic tube is gently passed into the lumen of the urethra to reach just beyond the palpable swelling. The obturator is withdrawn and the lighting circuit is then completed. As the tube is gradually withdrawn outwards the wall of the abscess will bulge into the lumen of the tube, and the opening of the gland-duct may show a little pus oozing from it. A small curved bistoury mounted on a long handle is passed through the tube, and the bulging wall of the abscess is freely incised, the pus is evacuated from it, and the pus-sac cauterised with tincture of iodine or the electric cautery. This is a more satisfactory procedure than puncture and aspiration of the pus-sac from without, and subsequent injection into it of a 1 in 20 solution of tincture of iodine. Local applications may be applied externally in the form of a hot fomentation of 5 per cent magnesium or ammonium sulphate. This will tend to reduce the œdema and lessen the subsequent pain. During the twelve to twenty-four hours subsequent to operation, local antiseptic treatment by injection or irrigation should be withheld.

As this condition is often the precursor of stricture formation, solid or expanding dilators up to a good size should be passed when the condition has healed, and the area of operation should be carefully examined by the urethroscope for dilatability before discharging the patient as cured.

Soft Infiltration of the Urethral Mucous Membrane.—This condition develops round the openings of the gland ducts and in the lacunæ of Morgagni, and is the result of a hyperplasia of the subepithelial connective tissue, causing a peri-urethritis. The overgrowth of connective tissue is at first symptomless, unless it be that there is some desquamation of the epithelial covering over the area causing threads to appear in the urine. The condition is painless.

Diagnosis.—The passage of an acorn-tipped bougie or of a straight sound often imparts to the patient and to the surgeon a feeling of resistance and irregularity on the mucous surface. The urethroscope is, however, the most certain method of diagnosis, and when viewed through it, the urethra is observed to have lost its lustre in places; its

striations appear to be irregular, and it does not dilate and collapse equally at the infiltrated area.

Treatment.—The treatment is essentially dilatation. By this means the newly formed fibrous tissue is broken down and the part vascularised. Kollmann's straight dilator is the best instrument for the purpose but must be used gently. Gradual dilatation is always preferable to more forcible work. If not treated the condition gradually develops into a hard infiltration or stricture—a not uncommon sequel of chronic gonorrhœa.

Cowperitis.—This condition, especially the subacute type, is more frequent than is commonly supposed. The duct on the left side opens on the floor of the bulbous urethra further forward than that on the right and is more often infected.

Symptoms.—There is little if any urinary disturbance, but pain is felt in the perineum, and often on the inner sides of the thighs, especially on sitting down or getting up. As the inflammatory process subsides the pain is more in the nature of a chronic aching. Intermittent urethral discharge continues to appear, and the urine is hazy and may contain threads.

Diagnosis.—The enlarged gland can be felt on rectal examination between the forefinger passed into the rectum and the thumb at the side of the perineal body externally. Normally the gland is not palpable by rectal examination.

Course and Treatment.—Rest in bed and soothing applications to the perineum, combined with gentle antiseptic treatment of the urethra, generally cause the condition to subside. Hot hip baths and the external application of glycerine and ichthyol 10 per cent, or lead and opium fomentations, help to reduce the pain and swelling. If the symptoms are severe all local intra-urethral treatment should be suspended for a time. If the condition does not tend to clear up spontaneously with this treatment the skin over the perineum soon becomes red and inflamed and there is considerable bulging in the perineum. When this occurs the gland should be incised under local or general anæsthesia, the pus evacuated, and the wound cauterised and packed with iodoform gauze. Subsequently a suppository of morphine gr. $\frac{1}{4}$ and atropine gr. $\frac{1}{75}$ may be administered.

In most cases healing quickly occurs subsequent to open incision. If the condition does not heal, or if it is allowed to point on the surface, a urinary fistula or retention cyst may develop, both of which are troublesome to cure. Complete excision of the gland is essential if either of these conditions develops, and is the only satisfactory method of eradicating the infection.

Infection of Para-urethral Canals.—These openings are by no means constant, and often do not connect with the urethra.

Tyson's ducts open on either side of the frænum in the coronal sulcus, while in other subjects small para-urethral ducts open just inside the meatus, and are a frequent source of chronicity in cases of hypospadias.

The best method of dealing with such infected areas is to incise and cauterise the canals or to destroy them by means of the electric cautery.

Prostatitis.—The prostate gland is affected in practically all cases of posterior urethritis because of its situation and its close connection with the posterior urethra.

Primarily the gland-ducts are affected by direct extension of the infection from the urethra. The infection spreads to the alveoli, and the peri-alveolar tissues become infiltrated with cellular deposit.

Symptoms and Diagnosis.—The condition is always a relative one, varying with the virulence of the infecting organism and the resistance of the patient. It may be an acute or subacute process, and it is only when the gland-ducts become blocked that the hyperacute condition of prostatic abscess with resultant retention, frequency and hæmaturia develops. Any of these conditions may be followed later by the chronic condition, in which any one or all of the various parts of the gland or gland-ducts may be affected.

Prostatic Abscess.—In the hyper-acute condition which frequently goes on to abscess formation the temperature rises to 103° or 104° Fahr., micturition becomes painful and

often frequent, and retention may finally supervene. There is acute pain in the perineum and a feeling of pressure in the rectum. Supra-pubic pain, which may simulate an acute appendicitis, is often present, and the patient feels and looks acutely ill. The urethral discharge in such cases temporarily lessens in amount or may cease altogether until the abscess has burst into the posterior urethra. The urines as seen by the two-glass test are both cloudy and contain comma-shaped threads which are characteristic of prostatic infection. These threads are plugs which have formed in the openings of the prostatic ducts and have been displaced in the process of voiding urine. The diagnosis is confirmed by examination per rectum, when the prostate either on one or both sides is felt to be enlarged, tense and very tender.

Treatment.—All intra-urethral treatment should be suspended and the patient put to bed. A purge of calomel gr. ii., followed by magnesium sulphate, should be given. Hot hip baths for fifteen to twenty minutes repeated four-hourly, and the subsequent administration of a morphine suppository gr. $\frac{1}{3}$ will temporarily relieve the condition and often enable the patient to pass urine, if retention has been a prominent symptom. Hot rectal douches at a temperature of 110° to 115° Fahr. act more quickly. If the patient cannot pass water subsequent to either of the above measures a soft rubber catheter may be passed and the urine drawn off, but this procedure should be avoided if possible. Expectant treatment by sedative lotions to the perineum and by suppositories to ease the pain is not to be recommended if there is complete retention and abscess formation is definite. The passage of a sound into the prostatic urethra and subsequent massage of the gland per rectum on the sound, with a view to causing the abscess to burst into the urethra, is often followed by a re-accumulation of pus in the cavity, which does not drain well. It is a method which cannot be too strongly condemned. Incision of the abscess per rectum has been supported by Oraison and others, but it is very liable to be followed by a rectal infection, and the operation, though an easy one, cannot be recommended on account of this danger, and also on account of the subsequent one of prostatico-rectal fistula. The most satisfactory method of treatment in the true prostatic abscess is to open, empty and drain the abscess through a curved perineal incision in front of the anus, as suggested by Zuckerkandl. With the patient in the lithotomy position an inverted V-shaped incision is made and the perineal body is defined. The transverse perineal muscle is retracted upwards, and on separating the fibres of the levator ani muscle the bulging wall of the prostatic abscess often comes into view. A finger is passed into the rectum and guides the blunt dissection along the anterior wall of the rectum, injury to which must be carefully avoided. The posterior wall of the prostate is exposed and opened by sinus forceps or by a vertical incision. The finger is then inserted into the abscess, and care taken to break down all the loculi and all collections of pus with the exploring finger. The prostatic cavity is washed out with antiseptic and a drain of rubber dam is left in for four or five days. Local treatment of the urethra may be commenced immediately after the operation.

Immediate relief is given by this procedure, and the condition quickly heals up. Subsequent formation of fibrous tissue and thickening may be prevented by the administration of ichthyol suppositories per rectum, and by prostatic massage which should be instituted forty-eight hours after operation. After the condition has healed and the urethral discharge has ceased, prostatic massage should be continued for some time. At first it must be done gently and at intervals of three to four days. By this means fibrous thickening is prevented, and any pockets containing latent infective material are emptied and the parts vascularised.

In addition to clinical cure, several microscopic examinations of the discharge from the prostate and of the urine passed subsequent to massage should give negative findings before the case is pronounced to be cured. Negative findings culturally are even more valuable in deciding when the condition is cured.

Acute Prostatitis.—In this condition the gland-ducts only or the gland as well may

be involved. That the ducts alone are involved in many cases is evidenced by the fact that per rectum practically no enlargement, tenderness or irregularity of the gland substance can be felt, and yet the prostatic secretion on bacteriological examination shows gonococci.

In other cases tender nodular areas may be felt in one or both lobes, and the subjective symptoms of frequency, pain, etc., may be prominent. In others again the whole mass of one or of both lobes may be soft, boggy and tender though not greatly enlarged. In estimating the severity of the infection much depends on the stage of the inflammatory process at the time when the patient is examined by rectal palpation, and on the amount of peri-glandular infiltration which has occurred.

Symptoms and Diagnosis.—In all cases of prostatic infection the urines in both the first and second glass are cloudy and contain pus. Frequency is usually the prominent symptom. In every case of posterior urethritis it is a good practice to examine per rectum at the first examination to determine the presence or otherwise of a prostatic involvement and the extent of it. If this were done in all cases it would be possible to determine the effect of intra-urethral, rectal, and other medication which may be carried out prior to the beginning of prostatic massage, and to be certain whether the condition is an after complication of treatment or not.

Subacute Prostatitis.—This condition may follow on an acute attack with or without suppuration, or may be subacute from the start. The degree of involvement is always a relative one, and the condition may be symptomless. In many cases the infection is not due to a gonococcal infection only, and secondary organisms such as *B. coli*, diphtheroids, staphylococci, etc., are often associated with it. It is not a painful process, and gives rise more to urinary discomfort, malaise and neurasthenia, than to gross symptoms like frequency and retention. Nocturnal emissions are common, and the urine frequently contains pus and is cloudy in its terminal portion. The diagnosis is confirmed by tenderness, irregularity of contour, or enlargement on rectal palpation, or by the boggy, soft condition of the gland.

Treatment of Acute and Subacute Prostatitis.—Rest in bed is essential in the acute condition. Hot hip baths or rectal lavage should be given frequently, and the administration of alkaline diuretics and sedatives, such as potassium citrate, potassium bicarbonate, hyoscyamus and buchu, relieve the condition considerably. If there is any enlargement of the prostate and pain is a prominent feature suppositories containing ichthyol min. v., antifebrin gr. ii., and atropine gr. $\frac{1}{100}$, are of considerable value in giving relief.

When the condition is very acute local treatment of the urethra should be withheld for the first few days. Subsequent to this lavage into the bladder may be begun, but never under more pressure than a height of 3 to 3½ feet, and with very mild solutions only; e.g. a solution of potassium permanganate 1 in 10,000, gradually increasing the strength to 1 in 6000.

When the inflammation has calmed down prostatic massage is the most effective method of getting the gland into a healthy condition, and is an essential part of the treatment if the infection is to be satisfactorily cleared up.

The massage when carefully performed acts in three ways:—

- (1) By emptying the infected alveoli and gland-ducts and so establishing drainage.
- (2) By causing a vascularisation of the prostatic tissues and so enabling the blood laden with antibody to reach the infected area.
- (3) By giving the patient an autogenous vaccine of his own living organisms.

There is no condition in gonorrhœa in which it is so essential not to be too energetic in the focal treatment as in prostatic massage subsequent to an acute infection, as there is always a big risk of setting up an epididymitis. The use of an atropine suppository, either before or after massage, helps materially to prevent this complication by preventing a retro-peristalsis along the vas deferens and the carrying of infection to the globus major and minor.

Prostatic Massage.—There is no more important procedure in the treatment of

gonococcal urethritis than massage of the prostate and vesicles. Except in very few cases it should not be instituted until such time as the acute inflammatory process has subsided, whether this process be in the urethra or in the prostate and vesicles. Clinically this is ascertained by the absence of turbidity in the urine by the two-glass test. The patient should be in the knee-elbow position, and the bladder should contain six to eight ounces of urine or of a clear antiseptic such as boracic lotion or chloramine-T, in order to obtain the best results with least discomfort to the patient. The forefinger of the right hand is covered with a finger-stall, well lubricated, and gently inserted into the rectum, while the left hand placed supra-pubically supports the bladder. Both lobes of the prostate gland and both vesicles are emptied by a gentle stroking from without, inwards, and downwards, and the finger finally stroked gently along the posterior urethra. It is advisable in most cases to allow an interval of three or four days before the succeeding massage. Severe pressure is not necessary, and there is no instrument which will do the work so satisfactorily as the palpating finger, or which will give such accurate information concerning the consistence and resilience of the infected part. In cases in which there are nodular areas of thickening in the substance of the prostate gland, pressure may be applied to these areas, and rotatory massage employed to break them down. If these methods are adopted the contents of the tubules and gland are expressed into the posterior urethra, and in addition to vascularisation of the part drainage is established and the whole posterior urethra brought into a much more healthy condition. While in many cases the expressed fluid will appear at the urethral orifice, in others it may fall back into the bladder, and in all cases the urine or antiseptic voided from the bladder subsequent to massage should be examined as well as the secretion expressed from the urethra. The process of massage is, as was stated earlier, essential in all cases of gonococcal infection and should be made a routine in the treatment of every case during the later stages of the infection. It must be persevered with until the prostatic urine and the prostatic secretion are clear macroscopically and free from pus cells on microscopic examination, or negative to cultural test. Only thus is it possible to be certain that a latent focus of disease has not been left in this part of the urethral tract.

Chronic Prostatitis.—Of all urethral complications this condition, more commonly than any other, gives rise to chronic gleet, general ill-health and neurasthenia.

Symptoms and Diagnosis.—A morning gleet, and occasionally emissions of semen during the action of the bowels, are the commonest signs. The urines, both in the two- and three-glass test, are usually clear, but may contain threads. On rectal palpation the prostate is found to be somewhat enlarged, irregular in its contour, and fibrous. There may be slight pain on pressure over the prominent areas, but not necessarily so. In other cases the gland feels soft and boggy but is not tender. The urine voided subsequent to prostatic massage is found to be turbid, and may contain prostatic threads. The patient complains of lassitude, malaise, and it may be vague arthritic and neuralgic pains.

Treatment.—There is no condition in which local antiseptic treatment is of less immediate value, as the infected area is beyond the reach of antiseptics. It is on this account that local applications of strong solutions of silver and similar preparations instilled into the posterior urethra with an Ultzmann's syringe are of so little value, unless prior to their use one effectively massages the prostate and vesicles. Even then their value is limited unless the infection is confined to the gland-ducts. The most effective local treatment is a course of prostatic massage at intervals of four to five days, and subsequent intra-vesical irrigation with antiseptics such as oxycyanide of mercury or chloramine-T in strengths of 1 in 5000. Irritating antiseptics are harmful, and are apt to set up a chemical urethritis. In general, patients are very apt at this stage to use the antiseptics prescribed in much too strong concentration, and they should be encouraged rather to increase the temperature of the irrigating fluid with a view to vascularising the part and stimulating the healing process. The massage should be persevered with until the urine voided after massage is clear and free from pus cells, and until on culture it

does not contain gonococci. If there is palpable enlargement of the prostate per rectum, or an irregularity of its surface which does not disappear with massage, drainage of the prostatic ducts may be assisted by suctioning the posterior urethra with a Mills' suction bougie. This instrument will remove the plugs of mucus from the prostatic ducts, will passively congest the parts, and so aid in resolution. This same end may be attained by dilating the posterior urethra carefully with a Kollmann's posterior dilator, but in doing so care must be taken not to injure the delicate mucous membrane with this instrument, and not to cause hæmorrhage. Before using these instruments it is advisable to give the patient urotropine internally in 5-grain doses three times daily after food with a view to preventing the setting up of a cystitis. In chronic prostatitis more than in any other condition detoxicated gonococcal vaccine helps to clear up the infected process and is the only certain method of getting directly at the invading organisms. Frequently, in addition to gonococcal infection, other organisms, such as staphylococci, streptococci, pneumococci, diphtheroids and bacillus coli are present, and if so it is essential to combine with the gonococcal vaccine a vaccine, autogenous by preference, of the other infecting agents. In giving vaccines in prostatic conditions it is not advisable to administer the vaccine at the same time as the massage is carried out, nor do cases of prostatic infection always tolerate with impunity the same high dosage as cases of purely urethral or joint infections. In all cases both the massage with subsequent irrigation, and the administration of an appropriate vaccine, should be continued until such time as the prostatic discharge and urine are free from pus cells and gonococci. While it may be difficult completely to eliminate the secondary organisms present, if they are not associated with the formation of pus, they can, in many cases, be ignored as saprophytes, and the patient considered free from gonococcal infection. In cases of this condition it is always very difficult to say that the patient is cured, and the standard of cure demanded should be a rigid one. Many of those patients remain carriers of disease over a long period, and in every such case an effort should be made—

1. To bring the prostatic tissue to its normal consistence and size.
2. To have the contents which are expressed from the prostate free from pus cells and gonococci after repeated examinations.
3. To obtain a similar condition in the centrifuged deposit of the prostatic urine, and to have it free from gonococci when cultured.

Spermato-cystitis (inflammation of the seminal vesicles).—As in prostatitis this condition may be acute, subacute or chronic, and may be due to the gonococcus alone or to secondary organisms combined with it. It is surprising that the seminal vesicles are not affected in a larger percentage of cases, and this may be due to the alkalinity of the spermatic fluid, or to the chemical nature of the internal secretion of the vesicles. When infection occurs acute abscess formation is rare. A cellular infiltration of the vesicle walls is more common. Subsequent peri-vesiculitis causes the opening of the common ejaculatory duct to become blocked and the vesicle to feel hard, tense and distended on rectal examination.

Symptoms and Diagnosis.—The symptoms in acute spermato-cystitis are often obscured by a concomitant acute condition in the prostate. In the greater number of cases the subacute or chronic form is present, and the condition, especially the latter, often passes undiagnosed, and is very resistant to treatment.

In the acute condition the urethral discharge may temporarily cease as in acute prostatitis, but not invariably so. The urines in the two- and three-glass test are hazy in all the glasses. Painful erections are common, and there is generally pain referred to the point of the penis immediately after the act of micturition and at times terminal hæmaturia. Frequency and urgency of micturition are prominent symptoms. On rectal palpation the vesicles are distinctly palpable and full of inflammatory deposit, if they are not masked by the accompanying prostatic enlargement.

In the subacute condition the urines in all three-glass tests are hazy, but the second

glass may be clear if the opening of the ejaculatory duct is blocked with muco-pus. On palpation per rectum the vesicles can be distinctly felt, and may be either soft and boggy, or may show areas of induration due to peri-vesiculitis. Pain at the end of micturition may be present, but is not a constant symptom in the subacute stage. Erections are generally painful.

In the chronic condition the urine may not show any signs in either the two- or three-glass test. Erections may be painful but not necessarily so, although they tend to be stimulated frequently in this condition. On rectal palpation the vesicles are not necessarily tender unless the palpating finger presses firmly on them; they are usually irregular in their contour and indurated, due to peri-vesiculitis. In other cases where the inflammatory condition is confined to the vesicle itself there are boggy areas to be felt on the surface. The diagnosis can be definitely confirmed by examining the expressed fluid from the vesicle on either side. The presence of pus in the vesicular discharge is at all times diagnostic of a pathological condition, and stained films may also show the nature of the infecting organism.

Treatment.—In the acute stage local treatment of the urethra should be suspended. The patient should be confined to bed, a saline purge or enema administered, and hot hip baths or hot rectal irrigations given two or three times daily. An alkaline diuretic containing potassium bicarbonate gr. xxv., potassium citrate gr. xxv., tincture of hyoseyamus min. xv., and infusion of buchu up to half an ounce should be given three times daily and suppositories of ichthyol gr. v., antifebrin gr. iii., and atropine gr. $\frac{1}{100}$, should be inserted per rectum night and morning. This treatment will in the course of twenty-four to thirty-six hours cause the acute condition to subside and the symptoms rapidly to ameliorate. As the condition becomes subacute the vesicle loses its tenseness and becomes less tender, but will still feel thickened and irregular in its outline to the palpating finger. Hot hip baths and the suppositories above mentioned should still be administered, and local treatment of the urethra may now be instituted, care being taken that in washing out the bladder the irrigating fluid is not raised to a height greater than three feet above the pelvis, and that it is not used in too strong concentration. In the course of eight or ten days of this treatment the urine will become clear, and as soon as this is attained, massage of the vesicles is indicated, and may be carried out at intervals of four or five days. The whole urethral tract and the bladder should be washed out subsequent to each massage. Even more so than in prostatic conditions the knee-elbow position is essential to enable the palpating finger to reach the upper and outer pole of the vesicle, and pressure should be exerted from without, downwards and inwards to evacuate the inflammatory products and detritus which have accumulated in the vesicles. As a prophylactic against infection of the vas deferens and epididymis, the administration of an atropine suppository gr. $\frac{1}{100}$, subsequent to massage is advisable, and in combination with ichthyol min. v., will accelerate the resolution of the inflamed organ. The massage must be continued until such time as the vesicles feel normal to the palpating finger, and until the expressed secretion contains neither pus nor organisms when examined microscopically.

There is no hard-and-fast line between the subacute and chronic stage of vesiculitis, and the treatment is essentially the same in the latter condition, with the exception that local antiseptic treatment is less indicated, and is only necessary subsequent to vesicular massage. In cases of chronic vesiculitis the instillation of silver nitrate 1 to 2 per cent, or of a similar drug into the posterior urethra or even into the ejaculatory duct by a Geraghty syringe, has been advocated with a view to setting up a reaction in the inflamed area, but the results of this method of treatment are not so satisfactory as are those obtained from vesicular massage and subsequent washing out of the whole canal. The administration of vaccine is a valuable adjunct to treatment in both acute and subacute vesiculitis, and even more so in the chronic conditions. It should be administered along the same lines as were advocated in the treatment of prostatic infections. Operative treatment has been advocated in certain cases of chronic vesiculitis. It is very rarely

necessary, and the results of vesiculostomy and vesiculotomy are not convincing. There are few cases that will not clear up when properly conducted massage and a detoxicated vaccine of the specific infecting organisms are administered, and routine treatment of the concomitant urethral infection is carried out.

Deferentitis.—Gonococcal infection of the vas deferens scarcely ever occurs as an entity by itself, and is generally accompanied and masked by an infection of the vesicle or epididymis. There are certain cases of vesiculitis and epididymitis in which the vas deferens seems to escape infection, although the organs at either end of it and with which its lining membrane is continuous are acutely inflamed. It may be that this is due to the nature of the secretion passing along the vas deferens, or to the fact that the epithelium lining it is ciliated and the secretions passing along it are so kept in constant motion. The symptoms consist of pain in the groin and a dragging feeling in the testicle, while the spermatic cord on palpation feels thickened and is tender to touch. The treatment is essentially the same as that of vesiculitis and epididymitis.

Epididymitis.—This complication is met with in varying percentages, the average being in about 6 to 7 per cent of cases. Some authorities put the incidence as high as 25 per cent, while others quote figures as low as 2 per cent. The incidence is dependent on the form of treatment adopted in the coexisting urethritis, and on the amount of exercise and physical exertion indulged in by the patient, who has in all such cases a posterior urethritis. It is primarily due to a direct extension of the gonococcal process along the vas deferens to the globus minor. This direct extension has been attributed by Oppenheim and Low to retro-peristalsis along the vas deferens. Among contributory causes to its onset may be mentioned too early instrumentation of a subacute case and too early and vigorous massage of the vesicles, or massage while the bladder is empty. Epididymitis does not arise from urethro-vesical lavage unless the irrigating fluid used is too strong and the flow of the fluid is under too great pressure. Indulgence in alcohol and sexual excess are apt to be followed by this complication, and are often contributory factors in its causation.

Symptoms and Diagnosis.—The condition develops during the second or third week of the infection, but may occur earlier, especially in an untreated case. The first symptom complained of is a dragging feeling and pain along the spermatic cord. There is a dull, heavy sensation in the testicle. The urethral discharge may disappear suddenly and the patient think that he is well. The pain in the cord increases gradually in severity and the structures around it become inflamed. The pain in many cases radiates up to the abdomen, and simulates very closely that of an acute appendicitis. The testicle becomes tense, swollen, tender and much enlarged, especially along its posterior border towards the lower pole of the epididymis or globus minor, while the skin over it appears red and inflamed. The temperature rises to 102° to 104° F. and the patient feels extremely ill and remains so until the condition is relieved by treatment. Whether the urethral discharge is profuse or temporarily disappears, the urines in both the two- and three-glass tests are turbid and full of pus in all glasses during the acute stage. Frequency is common as the result of the concomitant vesiculitis or prostatitis.

Treatment.—Treatment to be effective must be undertaken at once, and it is possible to abort the condition if appropriate measures are taken at the onset of the attack. Absolute rest in bed, the application of cold evaporating lotions or of an ice bag and support of the scrotal contents at the level of the abdomen, combined with the administration of a sharp purge and cessation of all intra-urethral treatment, will often cut short an attack. An injection of detoxicated vaccine containing five thousand million gonococci is very valuable at this stage in helping to cut short the condition, and often rapidly relieves the local tenderness and swelling.

Once the condition is fully developed hot applications are more soothing than cold, and are preferable. Lead and opium, glycerine of belladonna, or glycerine and ichthyol 10 per cent, are valuable sedative applications if they are kept closely applied to the

inflamed part. The best method of doing so is by fixing the dressings in position by means of an ordinary large triangular bandage with the apex of it split in two. The base is fixed round the pelvis and abdominal wall, and the ends are brought through between the thighs and tied in front to the base, thus keeping the dressing closely applied and at the same time supporting the scrotal contents.

The internal administration of salicylates has been advocated in Germany, and in certain cases gives good results when used in combination with the local application of a liniment containing methyl salicylate. During the last five or six years operative procedures have been advocated by various workers, the chief of which are as follows :—

(1) Puncture with a needle of fairly large bore into the globus minor, and aspiration by syringe of any fluid present. This in suitable cases can be performed without an anæsthetic, and in less than an hour gives relief to pain and tension. Apart from the damage which may be caused to the tubules it is not followed by any ill effects, although the operation itself is a painful one.

(2) Puncture of the surface of the epididymis with a sharp tenotomy knife at two or three points parallel to the tubules. This method acts in the same way as the first, but is not so liable to damage the small tubules. Without anæsthesia this also is a painful process.

(3) Open incision as practised by Hagner (epididymotomy). Under nitrous oxide anæsthesia the postero-lateral surface of the scrotum is incised down to the tunica vaginalis, the incision being about two inches long. The tunica vaginalis is then opened over the entire extent of the epididymis, and any areas of suppuration seen are punctured with a tenotome. About half a dozen punctures are made into the inflamed part to relieve the tension, but the incisions should not be deep enough to injure the tubules; a drain of rubber dam is inserted in the lower angle of the wound, and the various layers are stitched up with continuous catgut sutures. There is immediate relief of pain, healing occurs quickly, and in two or three days the drain can be removed and the wound allowed to granulate. In an acute case this method is preferable to either of the other methods mentioned previously.

(4) Vasotomy and subsequent injection of 20 per cent argyrol or other silver salt along the vas deferens. A blunt needle is inserted into the opening made in the vas deferens, and the argyrol solution is injected along the vas deferens towards the seminal vesicle. Although recommended by Helfield and Herbst, this method is not very satisfactory, and often fails to relieve the pain.

(5) Injection of electrargol $\frac{1}{2}$ to 2 c.c. into the substance of the epididymis is recommended by Asch. Collosol argentum is used in a similar manner. This method is valuable in the very early case, but in the established case it is not in any respect superior to puncture alone. The pain is markedly increased for a half to one hour subsequent to the injection, and then rapidly subsides. In a fully developed case the injection requires to be repeated two or three times at intervals of twenty-four hours, and is not always successful in clearing up the condition.

(6) Intravenous injection of sulpharsenol in doses of 12 to 24 centigrammes has been practised by certain French workers, and at times gives remarkably rapid results, as seen by the subsidence of the swelling, the lessening of pain, and the general improvement in the patient's condition. It is somewhat erratic, however, in its action, and cannot be relied on, while it seems to have no effect whatever on the concomitant urethral process.

While all these measures have their value in selected cases, the best results are obtained, in the early case, by rest in bed, the application of sedative lotions, and the administration of detoxicated vaccine. In the fully developed case the same treatment is indicated, but in addition immediate relief may be given to the pain by puncture of the epididymis by a sharp-pointed tenotomy knife, or by open incision as advocated by Hagner. It is noticeable that in the case treated by detoxicated vaccine the swelling and induration disappear more quickly. When these methods are adopted local treatment

of the urethra does not require to be discontinued for more than twelve to twenty-four hours, although care must be taken that the height of the reservoir of irrigating fluid is not more than three feet, and that the strength of it is not irritating to the mucous membrane.

There is no condition in gonorrhœa which responds so rapidly to vaccine treatment, and there are few cases of epididymitis in which any of the above surgical procedures are called for if detoxicated vaccine is administered early and the patient is confined to bed for forty-eight hours or more.

In cases which are seen late, and in which fibrous thickening of the epididymis and perifuniculitis have developed, the administration internally of iodide of potash combined with local inunction of unguent. hydrarg. co., or unguent. hydrarg. ammon., or the application of the former as a Scott's dressing, assists in lessening the induration, and in resolving the fibrous nodules so often present in the globus minor subsequent to epididymitis. Local treatment of the urethra by washing out the posterior urethra with mild antiseptics may be instituted as soon as the hyperacute condition has subsided. When the urines have become clear, prostatic and vesicular massage should be performed at intervals of three to four days, and subsequent to the massage washing out of the urethral tract is necessary.

During this treatment of the urethritis a good suspensory bandage should be worn. Massage of the prostate and vesicles is necessary, as these structures are practically always affected in a case of epididymitis. At first it should be performed very carefully and gently, and either prior to or subsequent to performing massage an atropine suppository should be administered to prevent retro-peristalsis along the vas deferens.

Either one or both vesicles are so often affected in a well-established attack that unless this part of the treatment is carried out as a routine, a great many cases will remain infective for a long time, and will recur later on.

In all cases before the condition is considered cured it is essential that the swelling of the epididymis and of the vas deferens should have disappeared, and in addition to this the urine passed after prostatic massage should be clear and free from pus cells, and the secretion itself and the urine should not contain either pus cells or gonococci on microscopic examination.

In a certain number of cases epididymitis is followed by sterility, and especially so if both epididymides are involved. It is common in untreated cases in which the acute condition may take a long time to resolve, and fibrous thickening frequently develops. If operative interference as previously mentioned is carefully performed, and if detoxicated vaccine is administered and the posterior urethritis attended to, the inflammatory process is reduced in its intensity much more quickly, and the fibrous thickening does not develop in and around the vas deferens and epididymis.

Cystitis.—This condition as a complication of gonococcal infection in the male is not so common as one would expect from the close connection between the bladder and the posterior urethra. When it does occur the part usually affected is the trigone of the bladder, and the symptoms are in all respects similar to those of a very acute attack of posterior urethritis.

Diagnosis and Symptoms.—Frequency and urgency of micturition accompanied by vesical tenesmus are prominent symptoms in the early stage. Micturition is painful, and the pain is usually referred to the point of the penis. In the three-glass test, the urine in all three glasses, and especially in the third one, is turbid, and often in the third glass blood is intermixed with the purulent urine. There is tenderness supra-pubically, and gonococci can be demonstrated in a catheter specimen of the urine. In the majority of cases there are other organisms present in addition to the gonococcus. *Bacillus coli* is the most frequent, and when this mixed infection is superadded to the gonococcal infection, the urine, which is at first acid, rapidly becomes alkaline in reaction.

Treatment.—Absolute rest in bed is essential, and hot hip baths help to relieve the

pain and tenesmus. The bowels should be emptied, and large quantities of bland fluid and very light diet should be given. Internally boric acid in gr. x. doses should be administered thrice daily in combination with urinary sedatives such as hyoscyamus and buchu.

In the hyperacute stage local treatment of the urethra must be withheld until the urgency and frequency of micturition have diminished, or have been allayed by the administration of a morphine suppository gr. $\frac{1}{8}$. A weak silver salt such as 1 in 5000 albargin or a solution of acriflavine, 1 in 4000 to 1 in 5000, should then be used to wash out the whole urethral tract and bladder. Mercurochrome-220 (1 in 4000) acts well. It retains its antiseptic potency in urine, and is well tolerated. This treatment, combined with careful administration of a specific detoxicated vaccine containing the infecting agents, will rapidly relieve the condition. After the acute stage the subsequent treatment is similar to that of a posterior urethritis.

Ureteritis, Pyelitis, and Pyelo-nephritis.—These conditions as complications are rare, and are not often met with in cases of carefully treated gonorrhœa where the resistance to the organism has been developed by suitable vaccine therapy, and the local inflammatory condition has been prevented from spreading to the bladder and by direct continuity to the ureter or the pelvis of the kidney. Cases may occur, however, in which the condition is due to either a lymphatic or a blood spread of the infection.

Symptoms and Diagnosis.—The close relationship between the ureter and the pelvis of the kidney makes it almost impossible to localise the infection to either of those areas, and in the greater number of cases the whole upper urinary tract is invaded. The acute condition is not a common one, unless the infection is very virulent or is hæmatogenous or lymphatic in its origin. The subacute or chronic type is more common, and is the result of a direct spread upwards from the lower urinary organs. It occurs chiefly when in the lower urinary tract there is an associated inflammation and obstruction to the outflow of urine. In such cases the infection is usually bilateral. The symptoms are generally slight, although the temperature may rise to 100° or 101° F. There is pain over the angle formed between the last rib and the erector spinæ muscle. The urine is often acid at first, and is heavily laden with pus. There is an excess of renal epithelium in the deposit from the urine, and the gonococcus can be demonstrated by culture from it. The pyuria is frequently intermittent. If there is an accompanying cystitis the urine may be alkaline, and night frequency is a common accompaniment. When the upper urinary tract is involved, the onset is sudden, and there is a much greater systemic reaction than with an infection of the lower urinary tract only. The final diagnosis is dependent on cystoscopic examination, when the orifices of the ureters will be seen to be inflamed and patulous, and a little pus may be seen oozing from them. Catheterisation of the ureters and subsequent examination of the catheterised specimen bacteriologically or by culture will confirm the diagnosis.

Treatment.—In the acute stage this consists of rest in bed, bland diet and free purgation. Internally one may administer urinary antiseptics or alkaline diuretics. Urotropine in 5 gr. doses or alkaline waters such as Contrexville or Evian may be tried. Local antiseptic treatment by instillations into the ureter and the pelvis of the kidney have been recommended, but are not without danger, and the results scarcely justify their use. Vaccine treatment should be tried in all cases, using small doses to begin with, and watching carefully the general systemic reaction. Attention must always be paid to the treatment of the lower urinary tract, and any stricture or obstruction to the outflow of urine dealt with and cleared up. The vaccine therapy should be persevered with over a fairly long period until the urine shows no pathological deposit and nothing on culture. If there are any signs or symptoms of abscess formation in the pelvis of the kidney, surgical measures may be necessary to relieve urinary obstruction or to establish free drainage from the kidney. The results of surgical measures are not always satisfactory, and all other means should be tried before resorting to them.

The treatment of the subacute and chronic condition is essentially the same, and the lower urinary tract must be carefully treated by washing out the bladder, and by removing or alleviating any obstruction to the urinary outflow, such as stricture, etc. Vaccine therapy gives good results, but care must be taken that the vaccine administered is a specific one and contains all the organisms which are contributory to the infective process, and the treatment must be carried out over a prolonged period.

Proctitis.—Rectal gonorrhœa is met with in women more than in men. The infection is commonly a direct extension from the vulvar orifice, or it may be the result of a direct primary infection following on sodomy.

Symptoms and Diagnosis.—The infection gives rise to very few subjective symptoms apart from slight pruritus, and there is never so profuse a discharge as is found in urethral gonorrhœa. The gonococcus can be demonstrated in the discharge.

Treatment.—If diagnosed early, local treatment will quickly eradicate the condition. Often, however, the diagnosis is not made before considerable ulceration and infiltration of the ano-rectal tissues have been caused, and a mixed infection by secondary organisms is usually then present. If the mucous membrane is damaged, local applications through the proctoscope are necessary, and at a later date treatment by rectal bougies must be carried out to prevent subsequent stricture formation.

Certain cases of suppurating Cowperitis and prostatic abscess in the male may point through the ano-rectal wall and infect this area. The treatment of these complications has been considered under these headings.

The same antiseptics as are used in urethral therapy are indicated in all ano-rectal infections, and in combination with vaccine therapy will clear up the infective process.

Adenitis and Lymphangitis.—In every case of acute gonorrhœa there is some inflammatory enlargement of the inguinal glands and of the dorsal lymphatics of the penis. Care should be taken not to confuse this condition with the adenitis due to syphilis. The enlargement of the glands is of quite a different character from that following on syphilis. The latter is a painless, quiescent process; the former is always tender to the touch, and there is more periadenitis associated with it.

No treatment is necessary apart from that of the infection of the urethral tract, and the inflammatory condition commonly disappears in twenty-four to forty-eight hours.

CHAPTER XLII

SYSTEMIC OR METASTATIC COMPLICATIONS OF GONORRHOEA

GONOCOCCAL ARTHRITIS: DIAGNOSIS, TREATMENT, TREATMENT OF ORIGINAL FOCUS—
BURSITIS—SYNOVITIS AND TENO-SYNOVITIS—MYOSITIS—NEURITIS—PERIOSTITIS—
PERI- AND ENDOCARDITIS—PLEURISY

Gonococcal Arthritis.—It is now generally conceded that this condition is due to a metastasis, the gonococcus being carried by the blood stream to the affected joints. Although this complication is more apt to occur in chronic gonorrhœa, or at any rate in the later stage of an acute attack, it may occur—and especially the polyarticular variety with an accompanying teno-synovitis—as early as the third day of the acute discharge.

Two varieties of arthritis are met with, an acute and a chronic process.

The acute type may manifest itself either as—

(a) An acute arthritis occurring in one joint only, but occasionally in two or three. The joint is swollen and tense, the skin surface over it is red and shiny, and the joint or joints affected are acutely tender on movement and palpation. This type of joint infection may go on to suppuration if mixed infection supervenes on the gonococcal process.

(b) A polyarthritis more often subacute and affecting chiefly the smaller joints of the hand and foot. The joints are tender, but not accompanied by so much redness and swelling as in the monarthritis described above.

(c) A diffuse arthralgia in which there are no clinical signs in the joint itself, but the affected joints are painful and the pain flits about from joint to joint.

The chronic type may manifest itself as—

(a) A hydrops articuli, usually monarticular, and occurring often in the knee joint. The affected joint is swollen and tense with fluid, but is not painful, and there is no redness on its surface. There may be limitation of movement.

(b) An osteo-arthritis, often multiple in character. There is in such cases a sero-fibrinous exudate into the joint, and, as a result of this, a marked tendency to the formation of adhesions and to subsequent deformity.

In both of the chronic types wasting of the muscles which act on the affected joints is a marked feature of the disease.

It is particularly noticeable in gonococcal joint affections that the acute types are more commonly met with during the acute or subacute stages of the concomitant gonorrhœa, while the chronic types are more often found as sequelæ to a chronic focus of infection in the posterior urethra, especially if the prostate and the vesicles are the site of the chronic infection.

In nearly all cases, both acute and chronic, the surrounding bursæ and tendon sheaths in close proximity to the joint are at the same time involved in the inflammatory process.

The gonococcus shows a predilection for attacking a joint which has been previously injured or affected by disease; and while the knee and ankle are the common sites in the

monarticular type, the polyarticular type more often attacks the metacarpo-phalangeal and inter-phalangeal joints of the hand and foot, and gives rise to a type of deformity described by Fournier as "radish finger."

Diagnosis.—In the acute condition there is rarely any difficulty. The gonococcus can be demonstrated in the accompanying acute urethral discharge, and the organism may be grown in culture from the affected joint fluid. In the chronic type the diagnosis is more difficult. The fact that the condition is monarticular, the history of a previous gonorrhœa, and the presence of a suspicious lesion in the prostate and seminal vesicles, point strongly to the gonococcus being the causal factor in cases of hydrops. The urethral discharge if present in any case should be examined and cultured, and the vesicular secretion should be investigated also. A positive gonococcal complement-fixation test is always present in gonococcal arthritis, and will, in doubtful cases, confirm the diagnosis. In osteo-arthritic cases X-ray examination is helpful in addition to the above methods.

Treatment.—In every case this must be twofold, and necessitates local treatment of the affected joint, and in addition treatment of the primary gonococcal focus.

In treating the affected joint the first indication is to relieve the pain, and for this purpose absolute rest is essential during the acute stage. The joint may be fixed if necessary by the aid of a splint of poroplastic or other material. An evaporating lead lotion, or ichthyol and glycerine 10 per cent, is an excellent application. Antiphlogistine is very soothing and helps to reduce the swelling and inflammatory exudate. Internally the administration of salicylates may give some relief, but in many cases this is of no value whatever in relieving the pain.

In all stages of the disease, and even in those cases which are chronic from the start, Bier's congestion as a method of treatment gives good results.

In the acute stage the best results are obtained by applying the constricting bandage continuously for eighteen hours in every twenty-four. In the more chronic cases the application of the bandage twice daily for two or three hours at a time is preferable.

It is not advisable to continue absolute rest and fixation of the affected joint for any length of time, because of the danger of adhesions being formed. To prevent this complication gentle passive movements should be instituted as early as possible after the acute condition has subsided, and should be followed later by voluntary movement and massage.

Certain resistant cases are met with in which the swelling and pain persist in spite of quiescent treatment, and it may be found advantageous in such cases to apply to the affected joint an ointment containing 40 grs. of salicylic acid to the ounce of unguent. capsici. This acts as a useful counter-irritant, and does not blister the skin if applied for a half to one hour daily. Good results are also obtained by the application of iodox or a similar mild counter-irritant. In the subacute and chronic stages the administration of colloidal iodine or of large doses of potassium iodide internally assists in clearing up newly-formed fibrous tissue, and helps to prevent the formation of adhesions.

Treatment of the Original Focus.—In cases in which there is a concomitant acute gonorrhœa this must be treated energetically on routine lines. In chronic cases the focus of disease must be sought for and the case treated as one of chronic gonorrhœa. The focus of infection is commonly situated in the prostate and seminal vesicles, and nothing is more effective in eradicating it than a course of prostatic massage and subsequent washing out of the urethra, care being taken at each massage to empty the vesicles completely, in which the gonococcus frequently lies dormant for long periods. It may be that the focus consists of a chronic infiltration of the anterior urethra or an infection of Littre's glands, and in such cases the diagnosis will be made accurately by the urethro-scope. In these latter cases treatment consists of dilatation, suction, and other methods to clear up the existing focus of disease. It is only by treating simultaneously the original focus of disease and the joint lesion locally that success will be attained. In many of these joint cases the condition is a true metastatic one, and the gonococcus

can be demonstrated in the affected joint fluid. This fact makes it essential that gonococcal joint conditions should be treated through the blood stream in combination with other methods, and there are few conditions in which the results of vaccine administration are so striking or so effective.

When only toxic vaccines were available for use the good results obtained from vaccine therapy in gonococcal arthritis were attributed to protein shock, as similar good results were obtained at times from T.A.B. vaccine, anti-diphtheritic serum, horse serum, and other similar preparations which could not possibly have any specific action on the gonococcus. It was noticeable that the results from these non-specific remedies were better when large reactions followed their administration either intravenously or intramuscularly. As this happened also with vaccines, this supposition was to some extent confirmed.

With detoxicated vaccines protein shock is absent, and large reactions do not occur, yet the results obtained are consistently good.

The blood serum of the patients, which gives a positive complement-fixation test in gonococcal arthritis, shows from week to week, under the influence of a specific detoxicated vaccine, a rapidly increasing amount of antibody, and the joint lesions as rapidly clear up. In a large number of chronic joint conditions in patients who have had a previous gonorrhœa, the expressed contents of the prostate and seminal vesicles may not show the gonococcus, or may in addition to it show some other micro-organisms—for example, staphylococci or pneumococci, etc., or it may be these secondary organisms alone and numerous pus cells on microscopic examination.

In such cases the best results are obtained by administering a detoxicated vaccine of these organisms or an autogenous in addition to a gonococcal vaccine. These organisms of themselves may give rise to joint conditions, and a gonococcus vaccine of itself will not act as a specific antigen to a staphylococcal or other organismal infection.

While urethral infection is the common precursor of gonococcal arthritis, other conditions due to the gonococcus, such as ophthalmia, proctitis, vulvo-vaginitis, etc., may also be succeeded by a joint condition, and the original condition in such cases requires treatment at the same time as the metastatic infection.

Patients who are suffering from gonococcal joint conditions, especially of the chronic type, tolerate much larger doses of vaccine without showing a gross reaction than do patients with other gonococcal lesions. In the type of case which is of long standing, and in which there is often a sero-fibrinous exudate into the joint, the administration of one or two doses of 3 to 5 c.c. intramine intramuscularly twenty-four hours prior to giving a vaccine will often enhance the action of the vaccine. This procedure is also useful in any case which is not reacting as rapidly as one would expect to a specific vaccine. An intravenous injection of sulpharsenol acts in a similar manner, but sets up a greater general reaction. Electrargol behaves in a similar manner when given intravenously.

Bursitis, Synovitis, and Teno-Synovitis.—These allied conditions may occur independently or in association with arthritis. The common situations of bursitis and synovitis are the supra- and pre-patellar bursæ of the knee joint, and the bursa under the tendo Achillis.

Teno-synovitis is met with more in the extensor than in the flexor tendons, and the tendon sheaths of the wrist joint and fingers and of the tendo Achillis and tarsus are the more common sites of infection.

Pain in such cases is at first very severe, although there may not be much swelling. The limb should be put at absolute rest, and local applications of antiphlogistine or of lead and opium will relieve the pain. Massage and passive movement should be commenced as soon as possible to prevent adhesions. The original focus of infection in the urethra must of course be attended to. As in arthritic conditions, vaccine therapy is of great assistance in relieving the condition and in effecting a cure. Suppuration does not often occur either in the joint itself or in the bursæ or tendon sheaths, and only in

the presence of mixed infection. Such a condition requires immediate surgical interference to prevent complete destruction of the joint cavity.

Myositis.—Myositis in the form of lumbago is common in many cases of chronic gonorrhœa. It is difficult to estimate how much of the condition is due to a toxæmia and how much to an actual gonococcal myositis. The true gonococcal myositis is seen in the muscles of the thigh and calf in association with chronic joint affections of the knee. In many of these cases the wasting subsequent to the initial tenderness is more than can be accounted for by want of use.

The treatment consists of rest in the acute stage; in the later stages massage and exercises, combined with vaccine therapy, rapidly relieve the condition.

Neuritis.—A neuritis due to the gonococcus occurs chiefly in association with prostatic conditions. The sciatic nerve and the genito-crural nerve are affected, and in many cases the pain is particularly resistant to treatment. The symptoms simulate those of an ordinary sciatica, and are often severe. The treatment consists of massage of the prostate and vesicles, and the administration of a detoxicated vaccine of the organisms found on culture of the prostatic urine. Local applications and counter-irritation at the site of pain are usually valueless.

Periostitis.—Periostitis has been found associated with a gonococcal arthritis, but there are no authenticated cases published of osteomyelitis due to this organism. The treatment is the same as that of the associated joint condition.

Pericarditis and Endocarditis.—Pericarditis and endocarditis due to the gonococcus were first described by Ricord, and the organism has been cultivated from the blood stream by several authors and from post-mortem material taken from the diseased valves.

The condition often passes undetected, as the symptoms are very little different from those of an ordinary rheumatic infection. Rest in bed, treatment of the original focus, and vaccine therapy are the only means of treatment. Focal and general reactions must be carefully guarded against by giving small doses of vaccine to begin with, and it is necessary to continue its administration over a very long period.

Pleurisy.—As in pericarditis and endocarditis, the pleura may be infected through the blood stream by the gonococcus, and the organism has been cultivated from the fluid aspirated from the pleural cavity. The symptoms are similar to those of an ordinary attack of pleurisy, but there is usually very little fluid in the pleural sac. It occurs most commonly in association with a severe metastatic lesion such as epididymitis. Counter-irritation locally, and treatment of the original focus of the disease, combined with a course of vaccine therapy, are the best methods of treatment. The condition rarely, if ever, goes on to suppuration or empyema.

For further information on the various metastatic infections see Chapter XXIII.

CHAPTER XLIII

GONOCOCCAL AFFECTIONS OF THE EYES

CONJUNCTIVITIS, SYMPTOMS, TREATMENT—IRITIS—ULCERATION OF THE CORNEA— KERATITIS AND PANOPHTHALMITIS, TREATMENT

Conjunctivitis.—An acute gonococcal infection of the conjunctiva may occur in the newly-born child, and is then known as ophthalmia neonatorum. The infection may also occur in older children and in adults.

In the new-born child ophthalmia may be the result of direct infection of the eyes *in utero*. In such cases the membranes have ruptured and the amniotic fluid has become infected. The eyes show definite physical signs at birth, and are often completely destroyed. More commonly the infection occurs at birth following on actual contact of the eyes, in the process of birth, with discharges from the vagina, the urethra, or the Bartholinian ducts.

In these latter cases the infection shows itself in twelve to twenty-four hours, and if there are no signs of inflammation of the eyes until after forty-eight hours the infection is more probably due to contamination from the hands of attendants, and from towels, etc., coming in contact with the eyes.

In either case the condition is very acute, and, unless treated promptly, leads to serious results and often to complete blindness.

Symptoms.—Of the cases of conjunctivitis seen after birth 75 per cent are gonococcal in nature. The eyelids become swollen, and can be opened only with difficulty. The conjunctiva, both on its ocular and on its palpebral surface, is acutely inflamed, and there is a profuse purulent discharge from under the eyelids. Ulceration of the conjunctiva occurs rapidly unless treatment is energetic, and perforation and panophthalmitis quickly follow.

Treatment.—The treatment is essentially prophylactic. Accoucheurs, nurses, and midwives should always question the expectant mother regarding leucorrhœa, and, if there is any history of it, should take special precautions at the time of delivery to cleanse the vagina and vulvar outlet with antiseptics.

The teaching of Credé, which is now generally adopted, should be rigidly carried out not only in maternity hospitals but in private practice, or at least some modified form of it on similar lines. If this were part of the routine of every accoucheur and midwife the incidence of child-blindness would rapidly diminish, and might even be eliminated altogether.

Immediately after birth the eyes of the child must be cleansed with sterile cotton-wool and a solution of silver nitrate $\frac{1}{2}$ to 1 per cent, or of protargol $2\frac{1}{2}$ per cent, or of argyrol 5 per cent, dropped into each eye and left for a few minutes and then washed out with warm boracic lotion. This may occasionally result in a little chemosis, but this is negligible if the silver solution is washed out with boracic acid soon after the instillation of the silver salt. This chemosis can be avoided by the use of a colloidal preparation of silver, which is even more effective therapeutically, and can be used undiluted. If these pre-

cautions have not been taken, and infection develops, treatment must be both energetic and immediate.

The infected eye must be washed out with a 1 in 10,000 solution of potassium permanganate, or with $\frac{1}{2}$ per cent boracic acid, and subsequently four or five drops of colloidal silver (1 in 2000 strength) should be instilled into it. The colloidal silver is painless, and does not coagulate albumin. It is immaterial what mild antiseptic is used to wash out the colloidal silver or in the subsequent cleansing of the conjunctiva. In the acute stage it is of the utmost importance that the surface of the eye be cleansed almost every half-hour to prevent the accumulation of pus, which rapidly causes ulceration and subsequent destruction. Normal saline solution or weak boracic acid will equally well serve for this purpose. It is usually sufficient if, in addition to the half-hourly cleansing, the colloidal silver preparation is used night and morning.

If only one eye is affected care must be taken to prevent infection of the other. The prophylactic treatment with colloidal silver already mentioned should be carried out, and subsequently a Buller's shield applied to protect the sound eye from infection. In cases of ophthalmia neonatorum it is of the utmost importance to remember that the mother must necessarily be suffering from a gonococcal infection, and in addition to the treatment of the child the mother's condition should be attended to on the lines described in a later chapter.

In young children gonococcal conjunctivitis may follow on the use of towels, etc., which an infected person has been using, but more commonly it is met with as an accompaniment of a gonococcal vulvo-vaginitis in the child. In such cases the infection is carried direct to the eyes by the child's hands. The condition as seen in the young child is not usually so acute as in the new-born infant; nevertheless it requires immediate treatment to prevent ulceration and subsequent formation of leucomata.

It is amenable to treatment if taken early, and the treatment is on similar lines to that of ophthalmia neonatorum.

In the adult two types of conjunctivitis are met with as the result of gonococcal infection.

In the first type the eyes may be infected by the hands of a person suffering from a gonococcal urethritis or vulvo-vaginitis. This condition is rarely seen in cases of urethritis which are under treatment, as patients are or should always be warned of the danger of not cleansing their hands while they are suffering from this condition.

The eye condition is very severe, and is marked by pain, photophobia, swelling of the eyelids, and rapidly developing purulent discharge from the surface of the eyes and eyelids.

Iritis, ulceration of the cornea, keratitis and panophthalmitis follow if the condition is not immediately brought under treatment.

Treatment.—As in ophthalmia, the washing of the surface of the eye and subsequent instillation of the colloidal silver must be carried out as early as possible, and subsequent to this the eye should be washed out every two to four hours with a saturated solution of boracic acid or with a solution of 1 in 10,000 perchloride of mercury. The application of the silver solution twice daily and repeated lavage of the surface will rapidly relieve the condition in most cases and prevent complications.

Both in ophthalmia neonatorum and in a conjunctivitis of gonococcal origin occurring in young girls and adults the administration of a detoxicated vaccine is a valuable adjunct to the local treatment, and assists materially in reducing the pain, in lessening the severity of the process, and in clearing up the infection. It is possible in the case even of the new-born child to administer with perfect safety to the patient a dose containing five hundred million detoxicated gonococci, and the dose may be repeated and increased without giving rise to any severe reaction, either local, focal or general.

The second type of infection in adults is not so severe, and is usually metastatic in nature, the organism spreading by the blood stream; in other cases the inflammation

may be a toxic phenomenon. In neither of these cases has the organism been isolated from the secretions of the eye, and this has led many authors to conclude that the condition is always a toxic one. It usually is seen in association with other metastatic complications, and especially with an arthritis of the vague flitting polyarthritic type. The condition of the eye is never severe, and comes and goes synchronously with the exacerbations of the urethral or of the joint condition. Toxic vaccines are apt to induce and aggravate the eye condition. There is always slight photophobia and a mild inflammatory reaction in the conjunctiva, but never a purulent discharge. The inflammatory symptoms quickly clear up with mild antiseptic treatment combined with the administration of a sensitised or detoxicated vaccine, which is necessary for the effective treatment of the original lesion.

For further information on gonococcal eye complications see Chapters XXII. and XXIII.

CHAPTER XLIV

GONOCOCCAL AFFECTIONS OF THE SKIN AND CONDYLOMATA ACUMINATA

ABSCESSES—TOXIC RASHES—KERATOSIS, SYMPTOMS, DIAGNOSIS, TREATMENT— CONDYLOMATA ACUMINATA, TREATMENT

GONOCOCCAL skin affections are comparatively rare, and may be grouped under the following heads :—

- (1) Abscesses.
- (2) Toxic rashes.
- (3) Keratosis blennorrhagica.

Abscess formation is uncommon, and is nearly always secondary to a lymphangitis of the penis. In a case seen recently a patient suffering from scabies had a scabetic run on the penis infected by the gonococcus although there was no accompanying urethritis. The risk of infection was admitted, and a pure culture of gonococci was grown from the lesion on the ventral surface of the penis. Open incision and drainage of the abscess rapidly cured the condition.

Toxic rashes are seen frequently in patients who have taken copaiba, therapion, and other similar preparations. In other cases the toxic rash may be the early erythematous stage of the condition known as keratoderma blennorrhagica. The rash may simulate that of any of the zymotic fevers, and may easily be mistaken for scarlet fever.

Keratosis is a rare condition. It occurs most commonly in conjunction with some severe metastatic complication such as arthritis.

Symptoms and Diagnosis.—The palmar surface of the hands and the plantar surface of the feet are the sites of election, and occasionally the rash may spread to the extensor surfaces, and may be seen on other parts of the body. In a case recently under observation the back showed very characteristic hyperkeratotic lesions, and, as often happens in this condition, balanitis circinata was present.

The initial lesion consists of a vesicle or papule with a horny centre which proliferates, as a result of leucocytic infiltration, until it becomes a limpet-shaped protuberance surrounded by thickened epidermis. When this crust is removed nothing is seen except a slightly reddened area of skin denuded of its epithelium. The most apt description is that of the French author who compared the protuberances to "mountains on a relief map." The lesions are always bilateral, and apart from the coexisting rheumatism are painless. Most of the cases are slight and show only one or two horny crusts, which disappear with treatment of the original urethral or prostatic lesion. Some few cases are very resistant to treatment, and the patient suffers from a pronounced toxemia, which is no doubt the cause of the lesion, although a case has been reported in which the gonococcus was cultivated from the skin lesion.

When occurring on the body the condition is apt to be confused with rupioid psoriasis, and when on the extremities with a hyperkeratotic syphilide. In the latter case the lesion is always unilateral, there may be other stigmata of syphilis, and the Wassermann test is

positive. In the former the lesions are not symmetrical, and there is not usually an associated joint condition or the history and evidence of urethral infection.

Treatment.—This consists essentially in treatment of the original focus of disease, which is situated commonly in the prostate and vesicles. Mild cases clear up effectually under routine treatment, and tonics internally of arsenic and iron are helpful in combating the toxæmia. In all the cases reported up to date the authors have spoken of the good results obtained from vaccine therapy in this condition. This is what one would expect from the toxic nature of the condition. Large doses of detoxicated vaccine are well tolerated by such cases and give remarkably rapid results. Good results have also been quoted by Bolam and Harrison from the intravenous injection of small doses of salvarsan in severe cases. Apart from the use of soothing applications, local treatment is of little value. As a local dressing the most effective is one of equal parts of eucalyptus and olive oil, which softens the crusts and prevents the skin from cracking.

Condylomata Acuminata.—Warty growths may and do occur in association with a gonococcal infection of the urethra, but are not necessarily gonococcal in origin. They are common on the inner surface of the prepuce, on the coronal sulcus, and on the glans penis, areas which are kept sodden and moist by the discharges or by a concomitant balanitis. They do not give rise to any pain, and are in the nature of simple papillomata. In certain cases there may be only one or two isolated warts, while in others the growths are profuse and vegetating.

Treatment.—The part affected must be kept as dry as possible, and any associated discharge treated along routine lines. If the warts are single the application of equal parts of liquor epispasticus and tinct. ferri perchlor. fort. will quickly remove the growth, and the application subsequently of a dressing soaked in the following lotion will prevent the appearance of any further warty growths. This application consists of vinum ipecac. 1 part, liquor arsenicalis 1 part, rectified spirit 2 parts. When the growth is almost cauliflower in nature and a large area is involved, the best method of treatment is to remove the warts with a sharp spoon under local or general anæsthesia. After removal the above lotion should be applied on strips of gauze. Bleeding subsequent to scraping is rarely profuse, and can be easily controlled by pressure, while there is less scarring subsequent to this method than with the use of the actual cautery.

Lactic acid may also be used to remove warts, but is not so effective as either of the above methods.

For further information on the above conditions see Chapters XXII. and XXIII.

CHAPTER XLV

NON-GONOCOCCAL URETHRITIS

SYMPTOMS ; DIAGNOSIS ; TREATMENT

AN acute inflammatory condition of the urethra may occur apart from gonococcal infection, and the signs and symptoms may often closely simulate an acute attack of gonorrhœa. The condition is commonly caused by the use of antiseptics for the purposes of prophylaxis against gonorrhœa. Trauma may also cause the condition, and certain organisms, such as the pneumococcus, the influenza bacillus, the diphtheroid bacillus, and others, may give rise to a urethral discharge.

Symptoms and Diagnosis.—Pain on passing water and a purulent urethral discharge are the prominent symptoms. The inflammation is rarely as severe as in a gonococcal infection. Whether the condition be due to trauma by antiseptics or other agencies, or whether it is the result of a micro-organismal infection, it is practically always confined to the anterior urethra, and often in traumatic cases tends to spontaneous cure. The diagnosis is dependent on the history and on bacteriological and cultural examination of the discharge.

Treatment.—In cases due to injury of the mucous membrane by irritating antiseptics or by instruments the condition is quickly relieved by rest, hot hip-baths and the administration of an alkaline diuretic. Local treatment of the urethra is contra-indicated. In cases due to infection by organisms such as a diphtheroid bacillus the same treatment is indicated, but in addition it is advisable to wash out the anterior urethra with a mild antiseptic such as chloramine-T 1 in 5000 or albargin 1 in 5000. In resistant cases it may be necessary to culture the causal organism, and to administer subsequently a course of autogenous vaccine. In those cases of urethral discharge which occur in association with an attack of influenza or other acute febrile conditions, treatment of the acute febrile condition practically always clears up the urethral symptoms. The fact that urethritis simplex does occur makes it essential that one should consider in every case the possibility of a urethral discharge being non-gonococcal. In all cases, and especially so in the case of a married patient, microscopic or cultural evidence should be obtained to verify the diagnosis.

See also Chapter XVI.

CHAPTER XLVI

GONORRHŒA IN THE FEMALE (IN GENERAL)

GENERAL EXAMINATION OF THE PATIENT ; SITES OF THE INFECTION ; METHODS OF INFECTION ; COURSE OF THE DISEASE ; METHODS OF DIAGNOSIS ; GENERAL TREATMENT ; MEDICAL TREATMENT ; LOCAL TREATMENT ; ABORTIVE TREATMENT ; LOCAL TREATMENT OF AN ESTABLISHED CASE

Gonorrhœa in the female was considered a simple vaginitis until Noeggerath in 1872 pointed out that it could be an ascending infection, and could affect not only the mucous membrane of the urethra and of the vagina, but also the epithelial lining of the uterus and of the Fallopian tubes and the pelvic lymphatics.

Although the infecting organism is in all respects similar in women, the disease tends to run a very much less acute course, and rapidly to assume a subacute form. It is this comparatively mild course of the disease that is its greatest danger in women. The patient is often unaware that she has contracted the infection, and does not seek advice and treatment in the early stages when the infection is easy to eradicate. The result is that treatment is not obtained until such time as the disease has involved one or more of the pelvic organs, and extended to parts beyond the effective reach of any local treatment.

There is a natural reluctance or shyness on the part of the female sex to call in their medical adviser in conditions which they always ascribe to menstruation, and if they have reason to suspect any venereal condition recourse is too often had to the promiscuous use of a vaginal douche.

One must also admit that many medical men when consulted by a female patient rarely examine their patient, either as to the history of the condition or for definite objective signs, and are quite content to prescribe an antiseptic douche for every patient who complains of a vaginal discharge.

Until this state of affairs is remedied and the treatment of both acute and latent gonorrhœa in the female is taken up seriously by the profession, the incidence, which is already large, will undoubtedly increase, and the gonococcus will continue to be responsible for a large percentage (some put it as high as 50 per cent) of the tubo-ovarian and other pelvic conditions which are seen in gynæcological wards, and for a great amount of the chronic ill-health from which so many women suffer.

The anatomical structure of the female genito-urinary organs makes diagnosis of this infection in the female much more difficult than in the male. On this account many patients who consult their medical advisers are wrongly informed that they are free from disease because there are no prominent signs of disease present. In other cases in which there is reason to suspect the presence of infection, a clean sheet is often given because of the absence of the gonococcus in the smear taken from the vulvar orifice. The gonococcus is not always to be found in the vaginal or vulvar discharge even in an acute or subacute infection, and rarely in a chronic one. The end result is that there are in existence a very large number of females who suffer little or no discomfort but who are definite carriers of the disease.

General Examination of the Patient.—As in the male, this cannot be too thorough. The history should be taken and the relation to menstruation of symptoms complained of should be inquired into, especially as regards painful menstruation. The time of onset of the vaginal discharge complained of should be ascertained, and information obtained as to whether there was associated with it pain or frequency of micturition. In the case of a married woman inquiry should be made regarding any previous pregnancies, and regarding the presence or absence of ophthalmia in the child's eyes at birth. With married women the questions must be put tactfully, and no suggestion should be made as to the responsibility of either partner for the condition complained of. Sterility, and especially one-child sterility, is always suggestive of a previous gonococcal infection.

For examination purposes the patient should lie on a couch in the Sims position, or be put in the lithotomy position on an examination table; and a good light is essential. The lithotomy position gives the examiner a better view of the parts, and enables specimens to be taken more easily, although with the latter method the patient is more exposed than with the former. To put the patient at her ease, and with a view to safeguarding the medical attendant, a nurse or third party should always be present.

The clothing is loosened, so that the abdomen and pelvic organs may be examined bi-manually. Having examined the lower abdomen and noted any tender areas in the region of the tubes, ovaries or bladder, and any enlargement of the glands in the inguinal region or rash upon the skin surface exposed, the patient is then put in the Sims or lithotomy position, and the external genitals are carefully inspected in a good light. The amount and nature of any vulvar or vaginal discharge is noted. In addition any swelling or ulceration of the external genitals should be looked for. The labia majora are then separated, and the Bartholinian gland on either side palpated between the finger and thumb with a view to detecting any swelling or induration of the gland. At the same time the opening of the gland duct on the inner surface of the labium minus on either side is examined, and a specimen of any discharge from it taken for microscopic examination, and any redness round its opening or other pigmentation is noted. Having made a careful scrutiny of the external genitals, the urethral orifice is next examined, noting especially redness, ectropium, and the presence of any discharge. If there is no apparent discharge the forefinger of the left hand, protected by a glove, should be inserted into the vaginal cavity, and the urethra milked by pressure on it through the anterior vaginal wall with a view to expressing any discharge present. The lips of the meatus should be opened, and the mouths of Skene's ducts, which lie immediately within the orifice, should be inspected. Having cleansed the area round the urethral orifice, a specimen is taken from the urethral canal with a sterile platinum loop or with a fine dressed probe, with a view to examining any secretion present for pus cells and organisms. Having completed the examination of the external genitals and of the urethra, the vaginal cavity is next examined by the aid of a Cusco's or Graves bivalve speculum. Any areas of redness, and any crypts in which the infection might lodge, are looked for, and the vaginal portion of the cervix is examined for erosion and redness, the presence or absence of Nabothian follicles, and the nature and amount of any vaginal or cervical discharge. The vaginal portion of the cervix having been cleansed, a sterile platinum loop is inserted into the endocervix, and a specimen taken for microscopic examination of any secretion coming from the endocervix. The speculum is then removed, and two fingers of the gloved hand are inserted into the vagina and a bi-manual examination made of the uterus, the Fallopian tubes, the ovaries, and the pelvic tissues in general, noting the presence of pain, swelling, tenderness or fluctuation in any area.

In conducting the primary examination of a female patient it is essential, if the best results are to be obtained, that the patient should not have used a douche prior to reporting for examination.

In connection with the examination of the urethral orifice, and in considering the specimen taken of the discharge from the urethra, the value of the examination is con-

siderably lessened if the patient has passed urine within two or three hours or has used a douche prior to the primary examination. If either of the above contingencies have occurred, the patient should be given definite instructions not to douche and not to urinate for at least four to six hours before being examined, and the examination should be repeated the following day under circumstances more favourable for demonstrating the presence of the gonococcus.

If, in spite of suggestive clinical signs, and in spite of a history which points to a past gonococcal infection, the gonococcus cannot be demonstrated bacteriologically or by culture, the patient should be kept under observation, and the examination repeated under favourable conditions as soon as possible after the cessation of a menstrual period. If this examination also is negative, the administration of a dose of one hundred to two hundred millions of a polyvalent gonococcal vaccine may assist in bringing the gonococcus to the surface within the succeeding twenty-four to forty-eight hours. At other times, if one has reason to suspect an infection of the endocervix, the insertion into the cervix of a plug soaked in glycerine may bring the causal organism to the surface, and enable it to be demonstrated in smear or culture. The same end may be attained by using the cervical suction bougie of Mills and examining the suctioned contents microscopically. If all these tests are negative, the blood should be examined by complement-fixation test to eliminate the possibility of a latent gonococcal infection.

Sites of the Infection.—Initially in the female the sites of infection are the urethra and the cervix, the frequency with which each is attacked being about equal. From either of these areas the infection may spread to any part of the vulvo-vaginal surface, and frequently does so to the Bartholinian duct and gland, and to the various crypts and para-urethral canals at the introitus vaginæ. Once the cervix is infected the pathway is opened up for infection of any part of the genital tract, either by direct spread upwards along the endothelial lining, or by way of the lymphatics. In urinary infections the condition may spread upwards to the bladder, ureter, and pelvis of the kidney, but this is not so common as is the upward spread to the uterine adnexa in cases of cervical infection.

Methods of Infection.—While cases may be found in which the infection, even in the adult, is the result of contamination by infected towels, douche-nozzles, hands, etc., the majority are the result of direct infection of the genito-urinary tract following on coitus. A man suffering from an acute, subacute, latent or chronic gonorrhœa may cause an acute or subacute infection of the female, and *vice versa*. The severity of the condition in the infected person depends on—

- (a) The virulence of the infecting organism.
- (b) The resistance of the patient.

In the female the infection may be modified or otherwise in its severity by the presence in the genito-urinary tract of other organisms which are originally saprophytic in nature but which become pathogenic as soon as the gonococcus has attacked and denuded the mucous lining of the tract. The more common of these organisms—the staphylococcus, pneumococcus and the Gram-negative diplo-bacillus, the diphtheroid and coliform bacilli—are frequently found on bacteriological examination of a vaginal smear, and are also found in films taken from the endocervix and the urethra, and their presence materially influences the line of treatment to be adopted.

Course of the Disease.—The initial signs and symptoms of infection vary according to the site of the primary lesion, but in general the subjective symptoms and the clinical signs are much less severe and of shorter duration in the female than in the male. An infection of the female urethra is ushered in by slight frequency of micturition and a scalding sensation on passing water. On account of the excellent drainage from the female urethra these symptoms disappear in twenty-four to forty-eight hours, and under favourable conditions the urethral infection may clear up rapidly. In other cases the trigone of the bladder is infected by an upward spread along the urethral surface, and if the infection is at all severe the discharge may infect any part of the external genitals

or may spread to the vagina and cervix. In cases in which the cervix is primarily infected the subjective symptoms are slight in nature, although there may be associated with them a persistent subacute vaginal discharge, and this discharge also may infect any part of the vagina or vulva. In a considerable number of cases the infection spreads from the cervix direct to the upper genital tract, while in others it spreads by way of the lymphatics to the pelvic cellular tissues. In primary infection of the Bartholinian duct and gland the lesion may be confined to that area, but may extend upwards and involve any other part of the female genital tract. In the larger number of cases of female infection the course of the disease is subacute. The patient suffers little if any discomfort, and the condition rapidly becomes a latent or chronic one. In many cases the sufferer is unaware of the fact that she is infected and a carrier of the disease. As in the male, the infection may be carried to any part of the body by the blood stream or by the lymph stream, and give rise to metastatic conditions such as arthritis. More commonly a gonococcal infection of the female is the precursor of a period of general ill-health, of obscure and intractable menstrual troubles, and of chronic invalidism.

Methods of Diagnosis.—Under this heading may be included—

(a) The history of a transient acute attack of frequency of and burning pain on passing water. It may also be possible to obtain a history of exposure to infection a few days prior to the onset of these symptoms.

(b) The history of urethral or vaginal discharge either in association with or subsequent to the above symptoms.

(c) Clinical signs of present or past inflammation of the Bartholinian gland or duct, of the urethra, the vulva, the vagina or cervix.

(d) Bacteriological examination of the discharges from the Bartholinian duct, the urethra and the cervix, taken under favourable conditions, and repeated if necessary after the cessation of a menstrual period, or twenty-four to forty-eight hours after the administration of a provocative injection of gonococcal vaccine.

(e) Complement-fixation test of the patient's blood for gonococcal infection.

It is also helpful in the case of married patients to have information regarding the possibility of infection of the husband, and it may be necessary to examine the husband. A history of one-child sterility may also point to a possible previous gonococcal infection.

The value of the various methods of diagnosis will be considered in detail in discussing the infections of each part of the female genito-urinary tract.

General Treatment.—The general principles of treatment which have been suggested in the case of male patients are equally applicable in infections of the female, and especially so in the very early stages of the disease. Rest in bed is advisable during the first week of the infection, and there is no doubt that the excessive amount of walking and the consequent irritation set up in the parts tends to further the spread of the disease and to set up complications. It also gives rise to ulceration of the external genitals. Local cleanliness must be ensured, not only from the point of view of preventing the extension of the disease, but as a protection to other members of the household. Great care must be taken to destroy by burning all sanitary towels and dressings which are used to protect the clothing. There is no better method of obtaining local cleanliness than by using once or twice daily a hot sitz bath with a little weak antiseptic added to it. The addition of bicarbonate of soda to the antiseptic bath will lessen the irritation of the external genitals, and soothe them when they are already inflamed. The bowels should be kept open by the administration each morning of a saline aperient, and the diet should be chiefly a milk one. No highly spiced foods or condiments should be taken. Alcohol in any form is bad, in that it leads to sexual excitement, which must be avoided, and to local congestion of the parts.

Medicinal Treatment.—In addition to the daily evacuation of the bowels an alkaline diuretic of potassium citrate and potassium bicarbonate in combination with hyoseyamus and buchu tends to lessen the pain on passing water, and, by increasing the amount of

urine, flushes out the female urethral tract. The oleo-resin class of drugs are of little if any value in the treatment of female gonorrhœa. When the disease has become sub-acute or chronic, medicines have little or no effect on the gonococcal process and are not indicated.

Local Treatment.—The form of local treatment to be adopted must vary with the part infected. In vulvar, urethral and vaginal infections the same antiseptics may be used as in the male, and will ameliorate and clear up any focus of gonococcal infection with which the antiseptic can be brought into contact. In infections of the endocervix or of any part of the upper genital tract antiseptic therapy is of little, if any, value, apart from its property of cleansing the surface.

Abortive Treatment.—This is only applicable in the very early stages of the disease, when the condition is ushered in by slight pain on passing water and slight frequency. It is very difficult in the female sex to be certain of aborting the disease, as there are so many crypts in and around the vulvar, urethral and vaginal orifices in which the gonococcus may lie hidden. If, however, a case is met with in the very early stages, a colloidal preparation of silver applied locally is the most potent drug for aborting the condition. In its full strength (1 to 2000) it does not cause any irritation of the parts and does not give rise to pain, while it is sufficiently potent to kill the gonococcus. The technique to be adopted is as follows:—

After passing water the patient is placed in the lithotomy position and the external genitals are carefully cleansed with an antiseptic such as biniodide of mercury 1 in 10,000, or 1 per cent lysol. Special care must be taken to thoroughly cleanse in and around the urethral orifice. The urethra and the bladder are then washed out in a similar manner to that described in washing out the posterior urethra in the male. In place of the Janet nozzle the type recommended by Kidd is better adapted for female work. Potassium permanganate 1 in 8000 to 1 in 10,000 is the best general antiseptic to use for this purpose. Colloidal silver 1 in 2000 is then slowly instilled into the urethra with the same type of all-glass syringe as is used in washing out the anterior urethra in the male. If there is any sign of inflammation round the openings of Skene's ducts, a small quantity of the colloidal silver solution should be instilled into them with a blunt-pointed needle and hypodermic syringe, and a similar procedure should be adopted in the case of any other apparent para-urethral ducts or vulvar crypts. The openings of the Bartholinian ducts are treated similarly if there is any sign of redness or inflammation around them. This process should be repeated daily on three successive days, and if by that time one has not been able to extirpate the gonococcus the routine methods to be described later should be adopted and abortive measures given up. In addition to the local abortive methods above mentioned, the administration of a detoxicated vaccine will increase the patient's resistance and materially assist in aborting the infection.

In cases in which the cervix is primarily affected, either of itself or in addition to the urethra, abortive methods do not hold out any hope of success, and the same remarks apply to gross infections of the Bartholinian duct and gland.

Local Treatment of an Established Case.—There is no more difficult problem than the eradication of the gonococcus from the female genital tract. This is due to the anatomical structure and histology of the various organs liable to be involved, and it is on account of their complexity and inaccessibility that the value of antiseptics in the treatment of female gonorrhœa is so limited. See Plate XIX., Nos. 1 and 2. The methods by which antiseptic therapy may be employed are as follows:—

(a) *Antiseptic Sitz Baths.*—For this purpose a weak solution of lysol, a solution of 1 in 10,000 to 1 in 20,000 perchloride or biniodide of mercury, or a solution containing boracic acid and sodium bicarbonate, act equally well. The sitz bath must be warm enough to secure a temporary local congestion of the parts. This method of treatment is applicable and can be used in all cases, no matter what part of the tract is involved.

(b) *Solutions for Irrigating the Female Urethra and Bladder.*—Permanganate of zinc

or of potash acts equally as well in the female as in the male, and can be used in the same strengths. Acriflavine, 1 in 5000, is also of value, and is more effective than permanganate when there is a superadded secondary infection. The silver salts, especially albargin, about 1 in 5000, may be used, but perhaps the best irrigating solution for the female urethra is one of $\frac{1}{4}$ per cent to $\frac{1}{2}$ per cent aqueous picric acid, the only objection to its use being its tendency to stain the hands and clothing. Mercurochrome-220 is open to the same objection, but is very effective as a germicide.

(c) *Douching*.—This form of treatment is commonly employed in gonococcal infections, but is very limited in its therapeutic value. The only object one can with certainty attain by douching is the cleansing of the vaginal surface, which in many cases is not infected by the gonococcus. No matter how well administered, a vaginal douche, as such, cannot and does not in many cases reach the infecting organism. There is also with careless and forceful douching the constant risk of carrying the infection from the external genitals to the upper genital tract. Vaginal douching certainly does not reach the endocervix, no matter how carefully carried out, and its promiscuous use by patients suffering from gonococcal infections should be discouraged.

(d) *Dry and Moist Swabbing*.—This is the most efficient method of treating vulvar and vaginal conditions. The mops used for swabbing the surface are carefully wrung out of the selected antiseptic, and the whole of the external genitals and the introitus vaginae are stretched out and cleansed. A speculum is passed, and the same methods are applied to the vaginal surface and to the vaginal portion of the cervix, the rugæ of the vaginal wall being carefully unfolded so that no nidus of infection is left untreated. Perchloride or biniodide of mercury, eusol, permanganate of potash, acriflavine, weak picric acid, mercurochrome-220, or any other antiseptic, may be used for this purpose. The surfaces are left as dry as possible after swabbing carefully, and the parts are dusted with an antiseptic dusting powder, the most efficient being—

R.	Zinc. oxid.	gr. x.
	Bismuth. subgall.	gr. xx.
	Magnes. carb. lev.	gr. xx.
	Pulv. amyl.	ad. $\frac{5}{8}$ i.
	Misce.				Ft. pulv.	

This powder is dusted lightly on the surface, and in addition to preventing friction and irritation it helps greatly to absorb the moisture and to keep the parts from becoming sodden.

(e) *Local Applications to Infected Foci*.—Among the many drugs which may be recommended for local application either to the urethral surface, the para-urethral canals, the vulvar crypts, or to the endocervix, picric acid in alcoholic or aqueous solutions, the former by preference, is a most valuable preparation. The solution of picric acid may vary from $\frac{1}{4}$ to 1 per cent in strength. Tincture of iodine and absolute alcohol in equal parts is also a very satisfactory combination. Formalin 1 per cent solution in glycerine also gives good results. Acriflavine 1 in 1000 may be used, while iodised phenol in varying strengths is specially indicated in cases of cervical erosion.

CHAPTER XLVII

GONORRHŒA IN THE FEMALE (IN DETAIL)

VULVITIS, SYMPTOMS AND DIAGNOSIS, TREATMENT. BARTHOLINITIS, SYMPTOMS AND DIAGNOSIS. ACUTE BARTHOLINITIS. SUBACUTE OR CHRONIC BARTHOLINITIS, TREATMENT OF SUBACUTE AND CHRONIC BARTHOLINITIS. VAGINITIS, SYMPTOMS AND DIAGNOSIS, TREATMENT. VULVO-VAGINITIS IN CHILDREN, MODE OF INFECTION, SYMPTOMS, DIAGNOSIS, TREATMENT. URETHRITIS, SYMPTOMS, DIAGNOSIS, TREATMENT.

Vulvitis.—This condition is rarely met with in the adult as the primary focus of a gonococcal infection. In children it is the common situation and the first part of the genito-urinary tract to be infected. The disparity in the frequency of this condition in adults as compared with children is due to the fact that in the adult the vulvar orifice is covered with squamous epithelium which is resistant to gonococcal infection; in the infant the epithelium is more columnar in type, and much more delicate and liable to become infected. This latter condition will be discussed under “Vulvo-vaginitis in Children.”

Symptoms and Diagnosis in Adult Cases.—On inspection there is a marked œdema and redness of the labia majora and minora, and the inner mucous surface of these structures may be eroded. A profuse purulent discharge is apparent on separating the labia, and as a result of this purulent discharge there is frequently a dermatitis of the skin surrounding the vulvar orifice. The condition gives rise to dysuria, itching and burning pain on movement, and the inguinal glands become tender and enlarged. Associated with the condition there may be present a urethritis or Bartholinitis, conditions which render the diagnosis easy. Microscopic examination of the discharge for gonococci will, if positive, confirm the diagnosis, but inability to find the gonococcus in a film should not be taken as proof that the vulvar condition is not the result of gonococcal infection in some other part of the genito-urinary tract.

Treatment.—As the vulvar condition in the adult is almost always due to the irritation of the discharge arising from some other focus, treatment of this focus is essential and often leads to spontaneous cure. In other cases the mucous surface of the vulva may be eroded by the discharges passing over it, and several of the small mucous glands in the region of the vestibule may become chronically infected. Apart from a slight irritation at the vaginal and vulvar outlet these infected mucous glands give rise to few symptoms. On close inspection they appear as small eroded hyperæmic spots, and are palpable as small nodules. The essential treatment of the vulvitis itself is rest in bed during the acute stage, and local cleanliness by means of antiseptic sitz baths. The addition of bicarbonate of soda to the hip bath is helpful in easing the pain. Moist swabbing with antiseptics, and the subsequent application of dermatol as a dusting powder, is also an efficient method of treatment. In cases in which the vulva is very swollen and acutely inflamed, considerable relief may be given by applying a dilute solution of subacetate of lead on strips of gauze, which are inserted between the labia majora to prevent friction. In some cases it may be necessary to shave or clip the hair of the external genitals to ensure cleanliness, and to prevent the discharges from setting

up a seborrhœic dermatitis. When the condition has become more chronic and the mucous glands are involved, the best method of eradicating the infection is the application of the electric cautery to the eroded spots. If an electric cautery is not available, these small chronically infected foci may be eradicated by the application of tincture of iodine or electrargol through a fine, blunt-pointed hypodermic needle attached to a syringe.

Bartholinitis.—This condition is the most frequent complication of vulvitis. The gland duct is primarily involved, and the infection quickly passes to the gland itself. The condition may be acute, subacute or chronic, and is very difficult to eradicate. Nearly all inflamed conditions of the Bartholinian gland are primarily the result of a gonococcal infection, although the suppurative process which follows is due to a mixed infection. Whether the condition be a purely gonococcal infection or the result of infection by other pathogenic organisms, it is so commonly associated with gonococcal forms of infection as to be practically pathognomonic of gonorrhœa.

Symptoms and Diagnosis.—**Acute Bartholinitis.**—The condition is frequently unilateral. It is sudden in its onset, and appears either during the acute stage of a urethritis or cervicitis, or it may come on suddenly some time afterwards from the lighting up of a chronic focus of disease subsequent to sexual excess. The infected gland becomes enlarged, tender and hard, and can be palpated as a clearly outlined tumour of the size of a hazel nut situated in the posterior third of the labium majus. The whole labium soon becomes œdematous, and the swelling may extend to the labium minus and as far forward as the clitoris. The swelling increases in size, due to inflammatory exudate, and the tissues surrounding the gland capsule become indurated. The skin over the gland appears red and inflamed, the lobes and lobules of the gland become filled with pus, and fluctuation can be demonstrated. The pus may burst through the gland capsule and point on the inner surface of the labium majus, or it may track towards the perineum and open even into the rectum. In all cases which suppurate, the opening of the Bartholinian duct on the inner surface of the labium minus appears red and inflamed, and the gland duct itself is blocked by the mucopurulent exudate.

Subacute or Chronic Bartholinitis.—In this condition there may be present either—

- (1) An inflammation of the gland duct only.
- (2) Inflammation of the gland duct and the gland itself.
- (3) A non-suppurative adenitis.

In the first condition the only signs present on inspection are a hyperæmia round the opening of the duct, and possibly some slight erosion of the mucous membrane in this area. On palpation slight induration is felt in the gland substance itself, and there is little or no pain present. Pressure along the line of the gland duct may cause a small amount of muco-pus to exude from its opening, especially if the duct is blocked. In the second type the same symptoms are present, but in addition small nodular areas are felt on palpating the gland, and rather more purulent fluid can be expressed from the gland duct. The third type is rarely met with.

The diagnosis in all cases is confirmed by the fact that there oozes from the gland duct a purulent exudate which on examination contains gonococci, and even in cases where pus expressed from the gland duct does not show gonococci, the fact that the gland is palpable is always suggestive of a previous gonococcal infection, and it should be treated as such, since this is the most frequent site of latent infection in female gonococcus carriers.

Treatment.—During the acute stage the patient must rest in bed and the bowels should be well opened. After shaving the external genitals, evaporating lotions such as an alcoholic solution of lead and opium should be applied to the inflamed part. This may in some cases abort the condition, and the swelling may rapidly decrease in size and clear up. If it does not, or if there is any sign of fluctuation, the patient should be anaesthetised and the gland and gland duct should be completely excised. An incision is made on the inner surface of the affected labium, and the gland carefully removed

by blunt dissection without if possible bursting it; if, however, prior to the operation or during the removal of the gland the abscess wall should burst, the lining membrane of the abscess must be painted with iodine and as much of the capsule as possible removed to make certain that every focus of infection is cleared away. In all such cases the cavity should be curetted with a sharp spoon, and subsequently washed out or swabbed with equal parts of iodine and absolute alcohol and the cavity closed up by buried sutures. It is rarely necessary to leave a drain at the lower end of the incision, and only so in those cases in which the abscess has already burst before operation, and in which there is consequently considerable difficulty in being certain that all the gland structure and the capsule have been completely removed. It is on account of this latter fact that simple incision followed by the application of some caustic and subsequent drainage does not in many cases cure the condition. Subsequent to operation the treatment is similar to that of a gonococcal vulvitis.

Treatment of Subacute and Chronic Bartholinitis.—If the condition is that of a slightly tender hard circumscribed tumour, the gland duct with the gland itself and its capsule should be dissected out, care being taken to avoid button-holing the inner surface of the labium majus. If the duct alone is involved one may inject into it an astringent and antiseptic injection with a blunt-pointed hypodermic needle. Colloidal silver or tincture of iodine 5 per cent in absolute alcohol is a suitable preparation.

In the more chronic cases it may be necessary to slit up the duct with a fine tenotomy knife, scrape it and cauterise the surface, the cavity being subsequently packed with sterile gauze to allow it to granulate from the base.

In the very chronic cases where the duct and gland alike are involved and the whole process is simply a palpable mass of fibrous tissue, the only method of eradicating the focus of infection is complete excision.

General treatment by means of vaccines assists materially in clearing up the condition.

Vaginitis.—Inflammation of the vaginal mucous membrane was at one time regarded as the most characteristic manifestation of gonorrhœa in the female. In the adult it is now known to be much less frequent than either urethritis or cervicitis, to both of which it is often secondary. The rarity of the condition as a primary one in the adult is due to the fact that the lining membrane of the vagina is covered with squamous epithelium, that it contains very few glands, and that it secretes an acid substance which is bactericidal in nature. None of these conditions hold good in children, in whom a primary gonococcal infection of the vagina is fairly common. In pregnancy also and in the puerperium, when the mucous membrane is soft and the spaces between the epithelial cells are widened, the gonococcus may easily penetrate the lining membrane and produce a primary vaginitis.

Symptoms and Diagnosis.—In the acute stage there is a burning sensation and a feeling of weight in the vagina and perineum. The discharge, at first muco-purulent, soon becomes purulent and fairly free. Pain on passing water and frequency are often present, and there may be slight fever and malaise. The vaginal surface appears red and œdematous, and is covered with foci of suppuration. The parts are extremely tender, and when the infection has lasted any time the lining membrane becomes eroded and granular. The cervix is usually acutely inflamed, and the inguinal glands are enlarged and tender to touch. This acute condition may last for seven to fourteen days.

In the subacute condition the above symptoms are less marked, the vaginal surface appears more granular, the discharge lessens in amount and is not so markedly purulent.

When the condition has become chronic there is often little pain or discomfort apart from itching at the vaginal orifice, and a burning sensation after passing water. The discharge in such cases is more in the nature of a simple leucorrhœa, but the symptoms are accentuated and the signs aggravated prior to and after each menstrual period.

In acute cases the diagnosis is not difficult, as, in addition to the presence of an infection of the cervix or urethra, one can usually demonstrate the gonococcus in the

vaginal discharge. In subacute and chronic conditions it is often extremely difficult to demonstrate the gonococcus in smear preparations or cultures from the vagina, and the diagnosis is more dependent on the finding of the gonococcus in other situations such as the urethra and cervix. Short of bacteriological evidence, a history of leucorrhœal discharge from the vagina subsequent to an attack of urethritis and associated with pain and frequency of micturition is always suggestive. In those latter cases the administration at the end of a menstrual period of a provocative vaccine containing one hundred to two hundred millions of gonococci, and examination twenty-four hours later of the urethral, cervical and vaginal discharge, will often confirm the diagnosis.

A vaginitis of itself is not in the adult a serious condition, and usually clears up rapidly when the urethral and cervical condition is effectively treated. In some few rare cases the condition may become very chronic and give rise to the condition known as xerosis.

Treatment.—In the acute stage the patient should remain in bed, the bowels must be well opened, and hot hip baths should be given every four hours. A mild antiseptic, such as sanitas with the addition of borax or bicarbonate of soda, may be added to the bath. A careful examination is essential to ascertain whether the condition is secondary to an infection of the urethra or cervix, so that treatment may be directed to the original focus as well as to the secondary vaginitis. In all cases the diet should be light, and large quantities of bland diluent drinks should be taken.

If the cervix is not affected douching should be avoided, and even in cases in which the cervix is infected douching of the vagina, especially if it must be carried out by the patient herself, is never so safe and is not so effective as swabbing of the vagina with antiseptics and subsequent dusting with a drying antiseptic powder. The antiseptics used should be slightly astringent, and only potent enough to destroy the infecting organism without damaging the mucous lining. Aqueous solutions of picric acid $\frac{1}{2}$ to 1 per cent, or of acriflavine 1 in 5000, are very effective applications; corrosive sublimate 1 in 10,000, or potassium or zinc permanganate 1 in 8000, all act equally well as cleansing agents. It is of great importance in applying these solutions to be certain that the rugæ of the vaginal wall are stretched out so that no areas of infection are missed. If there are any eroded areas the application to them of picric acid 1 per cent solution in spirit, or equal parts of iodine and alcohol, is indicated. Subsequent to swabbing of the vaginal surface the dermatol dusting powder mentioned previously should be lightly dusted over the whole surface with an insufflator, with a view to keeping the parts as dry as possible, and so preventing the mucous lining from becoming sodden. The use of pessaries of protargol and similar substances in the acute stage is of doubtful value. When the condition is very severe it may be necessary to administer an opiate to relieve the pain. In certain cases when it is not possible for dry swabbing to be carried out, a simple antiseptic douche of 1 in 8000 permanganate of potash, or of formalin 20 min. to 1 pint of water, will help to soothe the condition and lessen the discharge. The patient must be instructed how to use the douche, and glass nozzles with side perforations are preferable. The antiseptic should be as warm as can be comfortably borne and the patient should be in a recumbent position with the hips slightly raised, and great care must be taken not to use excessive force in carrying out the operation. In using gravity apparatus the solution should not be more than two feet above the pelvis. When the condition has become chronic, local applications to the eroded part of the vagina are often necessary in addition to douching or dry swabbing. Picric acid 1 per cent in spirit, iodine and alcohol in equal parts, ichthyol 20 per cent in glycerine, or any of the silver preparations may be used. They act best if applied directly by the medical attendant, with the patient in the lithotomy or knee-chest position, and with the vaginal surface exposed through a speculum. Short of this the medicament may be applied in the form of tampons, two or three of which are soaked in the chosen application and placed in the vagina close up to and around the cervix. Even in the chronic stage the condition of the cervix and urethra must be

carefully attended to, and although the gonococcus is not demonstrable in the discharge, the patient must be kept under treatment and considered infective until the whole process is healed up and the vaginal surface restored to its normal condition.

In the chronic stages general tonic treatment of the patient, the administration of iron and strychnine, and a change of climate help to improve the patient's condition and hasten the curative process.

Vulvo-vaginitis in Children.—This condition is a very acute process and is practically always a primary infection of the vulva and of the vagina, although there may be associated with it a urethral infection. While the gonococcus is the common cause the condition may also arise from infection by other micro-organisms, such as the pneumococcus and the diphtheroid bacillus. Apart from microscopic evidence, cases due to organisms other than the gonococcus cannot be distinguished clinically from those of gonorrhœal origin. The infection may occur in young girls at any time prior to puberty.

Mode of Infection.—In very young children it may be due to contamination of the genitals during birth; this is rare, as the parts are usually well washed and cleansed immediately after birth. More commonly the condition is due to accidental infection by towels, napkins, sponges, thermometers, baths, etc.

The condition is very contagious, and in institutions, children's hospitals, and public schools is apt to spread rapidly. In older children the infection may be due to criminal assault by a person suffering from an acute or subacute gonorrhœa.

Symptoms.—The onset is acute, and is ushered in by a sensation of itching or scalding at the vulvar orifice, subsequent to which the parts become red, swollen, and inflamed. The glairy white discharge which at first appears soon becomes muco-purulent, and finally a greenish-yellow and offensive pus. The parts are tender to touch, the pain is increased on walking, and there is a constant desire to pass urine. The infection rapidly spreads over the whole vulvar surface, and involves the vaginal outlet, and may spread through the hymen to the vagina itself and involve the whole upper genital tract. This rapid spread is due to the histological structure of the mucous membrane of the infantile vulva and vagina, which, although it does not contain any glandular structures, is not protected as in the adult by thick layers of stratified squamous epithelium. In some cases the condition is less virulent, neither the swelling, the amount of discharge, nor the subjective symptoms described above being of such severity as to cause acute pain.

Diagnosis.—In the acute and subacute condition this is easy, as the gonococcus can be demonstrated microscopically and in pure culture. When the symptoms are less severe, accurate diagnosis may be difficult, but every case should be looked on with suspicion, and examined repeatedly by bacteriological methods to make certain that the infection is not missed. The cuti-reaction is at times of value as a diagnostic agent in such difficult cases.

Treatment.—When a case is met with, prophylactic treatment of all other children who have been in touch with the infected patient should be carried out. Smears having been taken of any vaginal discharge, a solution of colloidal silver in equal quantity of normal saline should at once be applied to the vulvar surface if there is reason to suspect contamination by clothing, towels, or any other method. The infected child must be isolated from all other children, and the greatest care exercised to prevent the spread of the disease. The treatment is in all essentials similar to that indicated in cases of adult infection, although the tender mucous membrane of the child is more sensitive than that of the adult and milder antiseptics must on this account be used. It may be necessary in the very acute stage to give the child an anæsthetic to enable the parts to be thoroughly cleansed. Cleanliness should be ensured subsequently by hot hip baths once or twice daily, and the parts should after each bath be carefully swabbed over or painted with $\frac{1}{2}$ per cent aqueous solution of picric acid or with half strength colloidal silver; permanganate of potash and the silver salts may be used for the same purpose. When the condition has involved the upper part of the vagina it may be necessary

to incise the hymen to gain access to the vaginal surface. In certain cases it is possible to apply local applications to the vaginal surface and to the cervix through a urethroscopic tube passed into the opening of the hymen. Douching is not effective for this purpose, and is dangerous in that infective material may be swept into the cervix and the upper genital tract involved in the infection.

In addition to local antiseptic treatment vaccines should be administered, and excellent therapeutic results are obtained by their use.

In older children the infection is a very difficult one to eradicate and is very apt to recur. In no case should there be cessation of treatment until the discharges have been examined with negative results on three or four occasions.

Apart from infections of the upper genital tract such as salpingitis and peritonitis, the condition is rarely followed by complications. A Bartholinitis such as occurs in the adult is rarely met with as a complication. In cases in which gonococcal salpingitis or peritonitis does arise in young children the condition is usually an inflammatory one, and rarely does actual suppuration occur. The inflammatory symptoms subside with rest in bed, and one must trust to the administration of vaccines over a fairly long period to eradicate the infective process completely. For further information see Chapters XVII. and XXII.

Urethritis.—The urethra is perhaps the commonest site of infection in the female genital tract, and if not primarily affected it becomes contaminated at some time during the course of the infection. On account of its anatomical and histological structure the infection is rarely so severe or so difficult to eradicate as in the male. As in the male there are a considerable number of gland-ducts leading off from the urethra, the chief of which are known as Skene's ducts, and infection of these gland-ducts may cause the condition to last for a considerable time, although giving rise to few signs or symptoms.

Symptoms.—The disease may be acute, subacute, or chronic. The acute condition is ushered in by a sensation of scalding on passing water, by frequency, and at times urgency of micturition. The discharge, at first mucoid, soon becomes muco-purulent, and is never so profuse as in the male. The lips of the meatus are everted and reddened, the vestibule quickly becomes inflamed and irritated as the result of the discharge passing over it, and a vulvitis is set up. Rarely are there any constitutional symptoms present unless the cervix is also involved. In the subacute stage the inflammatory symptoms are less marked, the frequency and pain lessen in twenty-four to forty-eight hours, and the discharge becomes less profuse. There is generally some ectropium at the meatus, and on separating the lips of the urethral orifice the openings of Skene's ducts may be seen as small congested areas, and pus may be caused to exude from them by pressure through the anterior vaginal wall. There may be slight recurrent attacks of frequency, but there is little, if any, constitutional upset apart from a gradual loss of health and occasional pelvic pain. In the chronic stage there are rarely any symptoms, but a little muco-pus may be expressed from the urethral orifice on massaging the urethra through the anterior vaginal wall.

Diagnosis.—In the acute stage the gonococcus can be demonstrated in the urethral discharge with comparative ease. This is more difficult in the subacute stage, and it may be necessary to make repeated examinations under the most favourable conditions in those cases in which there is no urethral discharge present, but a previous history of pain on and frequency of passing water. In addition to this, one must consider, in the case of married women, the history of any past illnesses the husband has suffered from, and if necessary ask him to submit himself for examination. The history of ophthalmia in children is an additional diagnostic factor, as is also the presence of other diplococcal lesions in any part of the genital tract. When the condition has become chronic the diagnosis is more difficult still, and it may be impossible to demonstrate the gonococcus in films of the discharge from the urethral orifice. Skene's ducts should be examined

carefully, and any secretion massaged from their openings examined microscopically and by culture; so too with the secretion expressed from the urethra by massage through the anterior vaginal wall. In a case of latent or chronic infection the most favourable period for demonstrating the organism is just subsequent to a menstrual period, and the administration twenty-four to forty-eight hours previously of a large dose of polyvalent vaccine will often bring the organism to the surface and intensify the clinical signs. In every case in which specimens are being taken for examination purposes urine should not have been passed for four to six hours previously. The appearance of the urine is not so helpful in diagnosis in the female as in the male, and, apart from the acute stage, there may be no urinary symptoms or signs of disease. When all other methods have failed in establishing the diagnosis the complement-fixation test and the cuti-reaction may help to establish the fact that a chronic urethritis is gonococcal in nature.

Treatment.—During the acute stage rest in bed, hot hip baths, scrupulous cleanliness, and the taking of large quantities of demulcent drinks quickly alleviate the acute process. The diet should be regulated as in the case of infections of the male. An alkaline diuretic mixture containing citrate and bicarbonate of potash helps to flush out the short urethral tract and wash away the purulent discharge. This mixture is also indicated in the subacute stage, but is not necessary when the condition has become chronic. Care should be taken to prevent infection of any other part of the genital tract by swabbing the external genitals and introitus vaginae with a mild antiseptic, such as 1 in 10,000 biniodide of mercury or 1 in 5000 permanganate of potash, and subsequently dusting it lightly to keep the parts dry. If the condition is confined to the urethra alone, douching should be avoided and the urethra treated by injections or irrigations similar to those used in the male. Injections are carried out with a small blunt-pointed Janet's syringe, and not more than one-half to one drachm of the antiseptic in use should be injected, the bladder having previously been emptied so that the antiseptic fluid may remain as long as possible in contact with the infected urethral surface. Better results are obtained, especially in the subacute stage, by washing out the canal as above, and by subsequently washing out both the bladder and urethral canal by intravesical lavage. The strength of the solution used and the antiseptics exhibited are similar to those used in treatment of the male, although on account of its histological structure the mucous membrane of the urethra is not so sensitive or so easily damaged as in the male. If Skene's ducts are affected, the antiseptic solution may be applied directly along their tract with a fine blunt-pointed hypodermic needle attached to the syringe. When the discharge subsides and the condition tends to become more chronic, it is essential, as in the male, to get the antiseptic in contact with the infected area, and for this purpose suction of the urethral canal to establish drainage, the passage of bougies, subsequent massage of the urethra through the anterior vaginal wall, and it may be the application of germicidal substances through a urethroscopic tube may all be necessary to clear up the infection. For such local applications equal parts of tincture of iodine and absolute alcohol, colloidal silver, or $\frac{1}{2}$ per cent picric acid solution in spirit are the best preparations. The same substances may be applied to Skene's ducts through a fine needle attached to a hypodermic syringe, and good results are also obtained by obliterating the ducts by a fine-pointed electric cautery. Subsequent to any of these manipulations the urethral tract should always be washed out. The urethroscope is valuable in the case of female infections both as a means of establishing an accurate diagnosis in chronic cases and for observation of the effect of treatment. Although infiltration and subsequent stricture of the female canal is not so common as in the other sex, it does occur, and in cases which are slow to clear up should always be looked for. Gradual dilatation by straight bougies is the most effective method of causing the infiltrate to be absorbed.

It is difficult to establish in a female urethritis a certainty of cure, and even in face of negative clinical signs and symptoms, bacteriological findings over a fairly long period should be consistently negative. The most important time to take specimens for such

examination is immediately succeeding one of the menstrual periods. The administration of a specific vaccine, detoxicated by preference, will materially assist in cutting short the infection. It also prevents the spread of infection to adjacent parts and prevents the onset of complications by rapidly raising the immunity of the patient. The dosage administered should be slightly less than in a similar infection in the male, and should be regulated and controlled by the reactions set up subsequent to its administration.

CHAPTER XLVIII

OTHER GONOCOCCAL COMPLICATIONS IN THE FEMALE

CYSTITIS, SYMPTOMS, DIAGNOSIS, TREATMENT. URETERITIS AND PYELITIS. PROCTITIS, SYMPTOMS AND DIAGNOSIS, TREATMENT. CONDYLOMATA ACUMINATA, SYMPTOMS, TREATMENT. CERVICITIS, SYMPTOMS AND DIAGNOSIS, TREATMENT. ENDOMETRITIS, SIGNS AND SYMPTOMS, TREATMENT. METRITIS. SALPINGITIS AND OVARITIS, SYMPTOMS, DIAGNOSIS, TREATMENT

Cystitis.—Infection of the bladder occurs more commonly in the female than in the male. It is the result of an extension upwards of the urethral infection, and affects chiefly the trigone of the bladder, although it may later affect the whole vesical mucous membrane.

Symptoms.—As it occurs chiefly during the acute stage of a urethritis, the symptoms may be masked by the accompanying urethral condition. In addition to frequency of micturition and pain both during and after the act of passing water, there is marked urgency. There is bearing-down pain in the suprapubic region, and this area is tender on palpation. Constitutional symptoms, such as increase of temperature and slight rigors, may be present. The urine is turbid and often acid in reaction, and there may be slight terminal hæmaturia. In the subacute or chronic condition the above symptoms are not so marked, but turbidity of the urine continues, and if, as frequently happens, the bladder has been infected by other organisms, there may be exacerbations of the condition and the urine may become alkaline.

Diagnosis.—In the acute stage the symptoms of acute urethritis in association with suprapubic tenderness are always suggestive of an infection of the bladder. The symptoms and clinical signs continue longer than in a case of pure urethritis, and the presence of blood in an acid urine which is loaded with pus is suggestive of involvement of the bladder. Gonococci can be demonstrated both in the urethral discharge and in the terminal portion of the urine.

In the subacute and chronic stages the diagnosis is more difficult. Cystoscopic examination is helpful in confirming the diagnosis, the mucous membrane in the region of the trigone appearing inflamed and granular, and in places showing definite ulceration. At this stage it is often difficult to demonstrate microscopically or to cultivate the gonococcus from any of the secretions.

Treatment.—Rest in bed and careful attention to the regulation of the bowels, combined with a bland diet, are indicated during the acute stage. Medicinal treatment is dependent on the reaction of the urine. In a purely gonococcal condition with an acid urine, alkaline diuretics are indicated. In the more subacute conditions and in those in which there is a superadded mixed infection and an alkaline urine, urotropine in five-grain doses or salol in similar doses gives the best results. Warm alkaline hip baths relieve the pain and ensure cleanliness of the external genitals. If frequency and urgency are severe, it may be necessary to administer a suppository of morphine to relieve the patient. As soon as the patient has obtained relief from the urgent symptoms the urethra and

bladder should be washed out with a mild antiseptic, in the same manner as recommended for irrigation of the posterior urethra and bladder in the male. The female urethra and bladder will tolerate rather more potent antiseptics than will the male, but it is rarely, if ever, necessary to increase the strength of the irrigating fluid beyond that recommended in the earlier chapters. It is unwise in washing out the female bladder, and also unnecessary, to pass a catheter to get the antiseptic to flow in, but it is of advantage that the nozzle of the Janet type which is attached to the gravity apparatus should have a double way opening and an outflow tube. If this type of nozzle is employed the bladder can be emptied and refilled without disturbing the patient's position on the operating table, and the antiseptic fluid is brought into contact with both urethral and bladder wall. When the condition has become chronic, it may be necessary in addition to vesical lavage to apply astringent and antiseptic preparations such as colloidal silver to the ulcerated surface of the bladder wall through a cystoscopic tube. In both the acute and chronic condition good results are obtained from the careful administration of autogenous and detoxicated vaccines. While the purely gonococcal infection is rarely a difficult one to clear up there is often considerable difficulty in eradicating other infections, especially that of *Bacillus coli*, and recurrences of the subacute symptoms are by no means infrequent.

Ureteritis and Pyelitis.—Ascending infection may occur in the female, but is infrequent because of the free drainage from the female urinary tract. The treatment is similar to that described for the same condition in the male.

Proctitis.—Infection of the ano-rectal mucous membrane may be the result of contamination of this area by the discharges from a co-existing genito-urinary infection, and is much more common in women than in men. It is met with as a complication both in infantile and adult infections, but it may occur as a primary infection due to malpractices.

Symptoms.—These consist chiefly of itching, bearing down, and pain in the rectum. The discharge is rarely severe. The condition is exacerbated by the action of the bowels, and tenesmus is often severe.

Diagnosis.—In addition to the possibility of demonstrating gonococci in the discharge and to the severe pain which is present, there is on rectal examination in the sub-acute or later stages of the infection intense irritation in the anal region, and condylomata acuminata later make their appearance. Painful fissures occur around the anal opening, and in the later stages of the infection ulceration and infiltration of the mucous membrane occur, giving rise later to the formation of stricture.

Treatment.—Cleanliness is essential, and hot hip baths tend to promote this and give considerable relief to the pain and irritation. Suppositories of morphine may be administered to prevent tenesmus, and a dusting powder should be applied to the external parts to keep them dry and prevent the discharge from setting up a dermatitis. When the acute stage has passed and the pain lessened, rectal douches of permanganate of potash made alkaline by the addition of sodium carbonate give good results. On account of the constant irritation set up by the faeces passing over the infected area, and by reason of the frequency of a mixed infection, the condition is very difficult to cure, and tends frequently to become chronic. For this reason treatment must be continued for a very considerable time, and it may be necessary in some cases to dilate, under an anæsthetic, the anal sphincter, and apply antiseptic solutions to any ulcerated area of the rectal mucous membrane. If ano-rectal lavage cannot be carried out, suppositories of ichthyol, iodoform, or of any of the silver preparations may be used.

Condylomata Acuminata.—Warty conditions of the external genitals and even of the vaginal surface occur frequently in association with gonococcal infection in women. The moist condition of the parts and the sodden condition of the mucosa favour their appearance, and the warty growths may involve the lower genital tract and extend to the perineum and adjacent surfaces of the thighs. They are not necessarily the result

of a gonococcal infection, and it may be difficult to isolate the gonococcus, especially when they are associated with a chronic infection. They occur, however, quite frequently in association with female gonorrhœa, and especially as a result of gonorrhœa during pregnancy.

Signs and Symptoms.—The part affected is covered with warty growths which may be discrete, but which more often form themselves into a large cauliflower mass. If single the warts usually have a pedicle, but this is not so marked when they aggregate together. The surface is often bathed in pus and the surrounding skin is œdematous and irritated, while the discharge very soon becomes offensive and foetid. The only condition with which they may be confused is that of condylomata lata, which are the result of a generalised syphilis, but the diagnosis is not difficult, as the latter have a very much broader base, are much less vascular and less painful; the *Spironema pallidum* can be isolated from the serum expressed from the base of condylomata lata, the Wassermann test is positive, and other evidences of syphilis are frequently present on the body.

Treatment.—The essential treatment is to keep the parts clean and dry. Having cleansed the surrounding area and protected the healthy parts with sterile vaseline, isolated warty growths may be removed by the application to their base of equal parts of liquor epispasticus and strong tincture of perchloride of iron. The affected surfaces in addition to being kept dry should be painted afterwards with the following preparation :

R. Liquor. arsenicalis	.	.	.	5ii.
Vin. ipecac.	.	.	.	5ii.
Spir. vin. rect.	.	.	.	ad 5i.
Misce.	Ft. pigt.			

When the warts are in large masses, the quickest and most effective method of getting rid of them is to give the patient a general anæsthetic and remove the whole mass with a sharp spoon, care being taken not to remove more than the warty excrescences and their base. Subsequent to their removal strips of gauze soaked in the preparation mentioned above will prevent recurrences of the growth and quickly heal the raw surface. Hæmorrhage is rarely excessive, and any area of hæmorrhage may be controlled easily by a Paquelin's cautery or the application of adrenalin. Subsequent treatment consists chiefly in treating and removing the cause of the moist discharges, and in keeping the parts dry and clean by the application of the compound dermatol dusting powder mentioned in the treatment of vulvitis.

Cervicitis.—Gonococcal infection of the cervix occurs as a primary infection in about the same frequency as infection of the urethra. It may also result as an extension upwards from any focus in the lower part of the genito-urinary tract. From the histological nature of the covering of the vaginal portion of the cervix with its resistant squamous epithelium this part is very rarely affected. The endocervix, on the other hand, with its lining of columnar epithelium, is very liable to be infected. Once the infection has reached the endocervix the disease may spread with comparative ease and rapidity to almost any part of the upper genital tract. The cervical infection may be acute, subacute, or chronic, and acute exacerbations occur frequently in the later stages and subsequent to menstruation. This is due to the fact that the gland-ducts and deep racemose glands of the cervix, which are lined with columnar epithelium and which penetrate almost to the muscularis mucosæ, frequently become infected. See Plate XIX., No. 1. The condition resembles a chronic litritis or prostatitis in the male in its tendency to recurrence and in the difficulty of eradicating it.

Signs and Symptoms.—In the acute stage the cervix is eroded, somewhat œdematous, and tender to touch. The erosion present round the external os gives the appearance of ectropium to the lips of the cervix, and there may be small purulent foci present on the vaginal portion. These foci are the result more of the irritation caused by the

endocervical discharge than of an actual infection of the vaginal portion of the cervix. A fairly profuse and purulent discharge may be seen oozing from the external os, and this is more marked in multiparæ, in whom the canal is more patent and the erosion of the vaginal portion more extensive. The gonococcus can be demonstrated in stained films of the discharge from the endocervix. Unless at the menstrual epoch, there is very little pelvic pain as the result of the infection, and constitutional symptoms are slight. When the condition has become subacute, the discharge lessens in amount and is less purulent in character, while the only subjective symptoms are those associated with the menstrual period—namely, dysmenorrhœa, and at times menorrhagia. In the chronic stage the discharge resembles more that of an ordinary leucorrhœa, the menstrual symptoms are still present, and on inspection the erosion of the cervix, though scarcely so acute as in the earlier stages, is common. Gonococci are difficult to demonstrate in the secretions from the cervix unless the patient is examined during one of the acute exacerbations which occur subsequent to a menstrual period. In addition to the above symptoms there is often in the chronic stages a history of ill-health, and the constant leucorrhœa with associated menstrual pain and menorrhagia often results in debility and anæmia. In some of the chronic cases the Nabothian follicles become cystic in nature, and the external os is infiltrated with fibrous tissue and hypertrophied and hard in consistence.

Diagnosis.—In the acute stage the inflamed and eroded appearance of the cervix, in association with other evidences of infection in the lower genito-urinary tract, points to a gonococcal infection of the cervix. This can be confirmed by bacteriological examination of the discharge from the endocervix, which practically always in this stage is positive. In the subacute and chronic stages the demonstration of the gonococcus is difficult. The most favourable time for finding it is when the films are taken subsequent to a menstrual period. It is essential to remember that a primary syphilitic sore in the region of the external os may closely simulate the erosion caused by the gonococcus, and dark-ground examination of the serum from the edge of the eroded area should be carried out if there is any reason to suspect syphilis either from the incubation period, the subacute nature of the condition, or the associated enlargement of the inguinal glands. Palpation also of the part will be helpful in differentiating between syphilis and gonorrhœa, the syphilitic erosion being less tender, harder, and less liable to bleed than that set up by the gonococcal discharge. The greatest difficulty is in the diagnosis of subacute cases of cervicitis where the erosion may be due to a co-existing endometritis and endocervicitis of simple origin, or to some trauma of the cervix at labour. In such cases the presence of an infection in any other part of the tract is helpful; and short of this, if there is any history suggesting a previous gonococcal infection, negative bacteriological findings must be obtained subsequent to two or more menstrual periods before eliminating the possibility of the condition being gonococcal. The insertion of a tampon of glycerine into the external os, and examination twenty-four to forty-eight hours later of the secretion from the internal os, is another valuable method in these cases of obtaining material in which one can try to demonstrate the gonococcus. Cultural methods, the complement-fixation test and the cuti-reaction will also help in the differential diagnosis between a simple, a syphilitic and a gonococcal cervicitis.

Treatment.—Unless the condition is seen in the very early stages local treatment holds out little hope of completely eradicating the disease. This local treatment may be compared with the abortive treatment of the urethra, and the technique which gives the best results is as follows :—

After placing the patient in the lithotomy position the vulva and external genitals are cleansed with a solution of I in 10,000 biniodide of mercury. A bivalve speculum is then introduced into the vagina and the vaginal wall is similarly cleansed with biniodide lotion by means of swabs soaked in the lotion. The greatest care must be exercised to ensure that all the folds of the vaginal wall are stretched out, and that the external os is cleansed of all mucoid or muco-purulent secretion. This having been done, a Playfair's probe

dressed with sterile cotton-wool is inserted into the endocervix and the mucus cleared from it; a second probe soaked in antiseptic is then inserted into the cervical canal just short of the internal os and the probe rotated to make certain that the antiseptic comes in contact with all the crypts and glandular openings of the cervix. Equal parts of iodine and alcohol, pure solution of colloidal silver, or $\frac{1}{4}$ to 1 per cent picric acid in glycerine, the latter being the more penetrating, are the best preparations to use for this purpose. Having done so, a small strand of gauze soaked in the same preparation is inserted into the cervical canal and left *in situ* for twelve or twenty-four hours.

If this method is repeated twice daily for three days, the infection, if it is a purely surface one, may be completely eradicated, although the case must be kept under observation until two or more menstrual periods have passed before considering the condition as cured. The number of cases in which this treatment may be applied with success is comparatively small, as the gonococcus very quickly proliferates in the subepithelial tissues and along the ducts of the cervical glands, and as a result the success of local therapy becomes limited. (See Plate XIX., No. 1) If the infection has penetrated beyond the surface, all one can hope to do is to cleanse the eroded surface, to kill any organisms with which the antiseptic may come in contact, and to cause by the slightly irritant action of the antiseptic a vaso-dilator action with resultant hyperæmia. The technique to be employed in such established cases is similar to that described above, but the solutions used do not require to be in such strength: $\frac{1}{4}$ to $\frac{1}{2}$ per cent picric acid, 1 in 4 to 1 in 2 colloidal silver in normal saline, equal parts of tincture of iodine and absolute alcohol, or 1 in 5000 acriflavine, are all suitable preparations, and their application to the lining membrane of the cervical canal in combination with moist swabbing of the vaginal portion is all that is required locally. If erosion of the lips of the external os is very marked, the careful application of iodised phenol will cauterise the eroded surface and stimulate the growth of healthy granulation tissue. When the Nabothian follicles are involved in the infection the application of the electric or of a Paquelin's cautery is the best method of clearing them up. If possible, the swabbing of the vagina and any local application to the endocervix should in the acute stage be carried out once or twice daily; in the subacute stage treatment on alternate days, or even twice weekly, is in many cases sufficient to ensure cleanliness and a healthy condition of the surface mucous membrane. Douching of the vagina, unless carried out by a well-trained nurse, is not advisable, as it is not effective in its action, and it must be remembered that the vaginal surface is much more sensitive than the cervical, and that weaker antiseptic preparations require to be used in vaginal than in cervical therapy. In advising the use of a vaginal douche for purposes of cleanliness in cases where the patient is not able to report daily for treatment, certain cardinal rules should be laid down: the patient should be in the lying or semi-recumbent position; the external genitals should be thoroughly cleansed; the douche can, rubber tubing, and glass vaginal nozzles should be carefully sterilised.

A glass nozzle with lateral openings, and not a terminal one, should be used.

After the antiseptic has been prepared and heated to a temperature of 104° to 106° F. the douche can should be raised to a height of two or three feet above the pelvis. The patient should then recline in a recumbent position on some waterproof sheeting, and the hips should be slightly elevated by resting on a douche pan. The labia are then separated and the glass nozzle is inserted well back into the posterior fornix, and the antiseptic douche allowed to flow in and out gently.

The most suitable preparations for this purpose are lysol $\frac{1}{2}$ per cent, potassium permanganate 1 in 8000, weak sanitas with the addition of a little borax, biniodide or perchloride of mercury 1 in 10,000 or albargin 1 in 5000. Subsequent to swabbing the vagina or careful douching, an absorbent dusting powder may be applied to the vaginal walls by means of an insufflator, the best combination being one of zinc oxide, light magnesium carbonate, bismuth subgallate, and powdered starch. When applied subsequent to swabbing, this antiseptic and healing powder will absorb moisture, prevent irritation

and ulceration of the opposing surfaces, and keep the patient much more comfortable. Vaginal tampons soaked in such antiseptic solutions as ichthyol are not of any great value in affections of the cervix, apart from the hyperæmia which they cause by reason of their acting as foreign bodies, and by their chemical action of stimulating the flow of blood to the parts.

In the more chronic cases of infection of the cervix, and especially when the gland ducts and the racemose glands are infected, the condition is extremely difficult to treat, and still more difficult is it to be certain that the condition is cured. In addition to cleanliness of the vagina and of the outer and inner parts of the cervical canal, it is essential to try to establish drainage of the infected glands and gland ducts. Two methods are applicable:—

(a) The introduction for twelve to eighteen hours into the cervix of small tampons soaked in slightly irritating fluids suspended in glycerine. Solutions of 1 per cent of picric acid, of 1 in 1000 acriflavine, or of 1 per cent formaldehyde, when so inserted, stimulate the flow of the serum to the surface, and help to establish drainage.

(b) The introduction of a small suction apparatus into the cervical canal, such as that recommended by Mills (see Fig. 22), with a view to passively congesting the cervical canal. This instrument is very effective in removing the pus plugs and in causing a

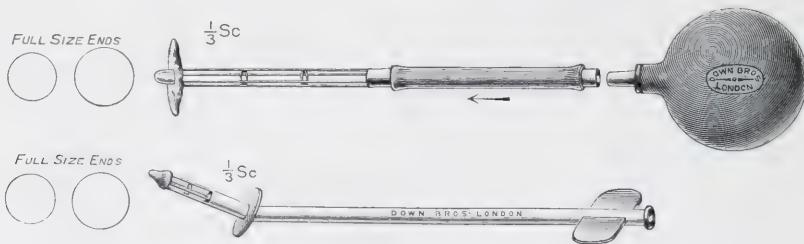


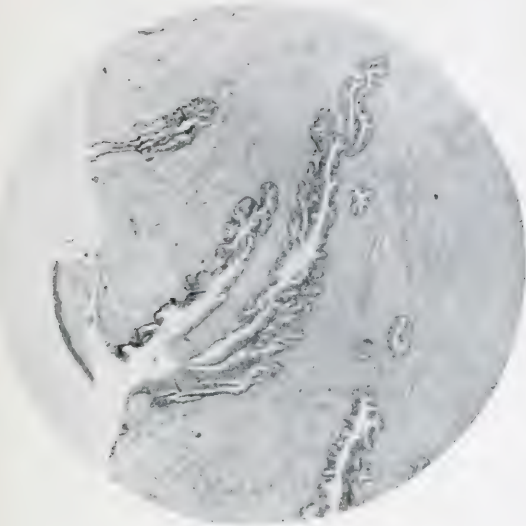
FIG. 22.—Mills' suction bougies for the cervical canal.

venous congestion. Subsequent to its use one may apply antiseptics to the cervical canal to destroy any infective organisms which have been brought to the surface.

In the treatment of acute, subacute, and chronic cervical infections the careful administration of a potent detoxicated vaccine is often of great assistance. The infection is so inaccessible in most cases to local therapy that the only hope one has of completely curing the condition is so to raise the patient's immunity by vaccine therapy as to render her capable of overcoming the toxic symptoms and finally the infective process. Patients with lesions of the cervix and upper genital tract react well to vaccine therapy if this therapy is specific and the dosage carefully regulated. To ensure this, it is essential in practically all cases, and more especially in the subacute and chronic ones, to combine the administration of a polyvalent gonococcal vaccine of known antigenic power with an autogenous vaccine of the organisms cultivated from the mucous membrane of the cervical canal. The combination of local cleanliness by the application of mild antiseptics to the surface of the canal and the establishing of drainage, aided by the administration of a specific vaccine, conjointly ensure the most rapid and most certain cure of any infection of the cervical canal and its associated gland structures.

Endometritis.—The lining membrane of the uterine cavity may become infected as the result of the extension of the gonococcal process from the cervical canal. From the close apposition of the cervical canal and the endometrium of the uterus, gonorrhœal endometritis should be a fairly common condition. There is no doubt that the endometrium is frequently infected, but the signs and symptoms of the condition are often masked by the accompanying cervicitis or salpingitis. In addition to this, drainage from the uterine cavity is good. These factors, in association with the resting condition of

PLATE XIX



No. 1.—Section of the cervix, showing a racemose gland.
Magnification, 25 diameters.



No. 2.—Section of the wall of the uterus, showing convoluted glands. Magnification, 25 diameters.
The gonococci in this case had penetrated as far as the peritoneum.



No. 3.—Section of the male urethra, showing that its wall is thrown into folds. Magnification, 25 diameters.

the uterus between menstrual periods, and its excellent blood supply, explain to some extent why gross symptoms of uterine involvement in gonorrhœa are so seldom present.

Signs and Symptoms.—The condition may be acute or chronic, the latter being the more common clinical entity. In the acute stage the patient feels ill, is feverish, and complains of pain suprapubically. Menstruation may be irregular, and is often excessive, both in duration and quantity. In severe cases the condition simulates an acute abdominal infection. There is always present a profuse discharge from the cervix. This is not so tenacious and glairy in character as that of a purely cervical infection; in the acute stage it is quite purulent and is often sanguineous. On bi-manual examination the cervix is found to be patent, soft in consistence and tender to touch, while the uterus itself is soft, enlarged, and tender. In many cases it is difficult to distinguish between endocervicitis and endometritis, and bacteriological examination of the discharge from the cervical canal, while confirmatory of a gonococcal infection, does not help to locate the site of the infection. Exacerbations of the purulent discharge subsequent to a menstrual period are always suggestive of uterine involvement. In practically all cases there is an accompanying infection of the lower urogenital tract. The diagnosis is difficult in cases which occur post-partum, and especially so subsequent to an abortion. In those conditions the most valuable diagnostic facts are the evidence of a gonococcal infection elsewhere in the tract and bacteriological investigation of the discharge from the cervix. The symptoms of a chronic infection of the uterus are much less marked, the chief one being leucorrhœa. The leucorrhœal discharge in endometritis is more thin and watery in nature than in a cervical lesion, and it is with difficulty that the gonococcus can be demonstrated in films of this watery discharge, unless under the most favourable conditions. Menstruation in most cases exacerbates the infection, and the period subsequent to its cessation is the most hopeful one in which to examine the discharge either microscopically or by culture. Menorrhagia, dysmenorrhœa, and metrorrhagia may all occur as the result of a chronic gonococcal infection of the uterus, and if any of these conditions are complained of by a patient who has a history of a past infection of any part of the genito-urinary tract or a co-existing infection elsewhere in the tract, the uterus is probably involved in the infective process.

Treatment.—In the acute stage the patient must rest in bed; the bowels must be well opened, and if necessary a small dose of morphine may be given as a suppository to ease the pain. An ice-bag applied to the lower abdomen will also assist in relieving the urgent symptoms. Douching should be avoided, and the vagina and cervix should be kept clean by swabbing with antiseptics as described in the treatment of cervicitis. When the condition has become subacute or chronic the treatment is on similar lines, but in addition one may with advantage increase the vascularity of the genital tract by inserting ichthyol tampons high up in the fornices subsequent to cleansing the cervical and vaginal cavities. Operative interference in the shape of curettage is rarely called for, and is not devoid of the danger of spreading the infection to the myometrium and the Fallopian tubes. The application of caustics to the cavity of the uterus does not aid materially in eliminating the infective process, and is very painful unless an anæsthetic is given. The best results are obtained by cleanliness, rest in bed, hot hip baths, and the gradual immunisation of the patient by means of detoxicated gonococcal vaccine. In the acute stage the initial dose must be small, and should be increased guardedly at intervals of five to six days. In the chronic stage the action of the vaccine is assisted by administering tonics such as arsenic to improve the general health of the patient.

Metritis.—This condition may occur in association with endometritis, and is a common result of operative interference. It may also occur subsequent to abortion or childbirth. The condition is difficult to distinguish from a pure endometritis, apart from the fact that a salpingitis is generally associated with it.

The treatment is essentially the same as that of the accompanying endometritis. In the chronic stage the treatment may be assisted by the administration of iodides.

Salpingitis and Ovaritis.—Gonococcal infection of the tubes and ovaries most frequently arises from an extension upwards of the disease from the cervix and uterus; it may also spread by the lymphatics of the pelvis or by the blood stream from the lower genital tract, and be metastatic in nature. In these latter cases there is usually a considerable amount of pelvic cellulitis.

Signs and Symptoms.—In the acute stage, when the condition is still an inflammatory one, the infection is ushered in by a feeling of chill and rigors. There may be vomiting, and the pain is referred to one or both iliac fossæ. The temperature is raised, the patient feels ill, and the condition, if severe, simulates that of an acute abdomen. The lower abdomen is tender on palpation, and may feel board-like. As the infection generally spreads to the tubes just subsequent to a menstrual period or to abortion, pain in the pelvis or lower abdomen occurring subsequent to either of these conditions should be investigated by examining bi-manually the contents of the pelvis. If gonococcal infection of any part of the tract is suspected clinically and confirmed bacteriologically, the chances are that the abdominal pain is due to a tubal infection or to an associated cellulitis. On palpation the uterus, tubes, and ovaries will be tender and enlarged, although the enlargement may not be a prominent one, unless actual pus formation has occurred in the tube and a pyosalpinx formed. If a pyosalpinx has developed, the affected tube will be felt as a boggy, fluctuating swelling lying close to the uterus or filling up the fornix and the pouch of Douglas on the affected side. Unless the condition develops into one of pyosalpinx through blockage of both ends of the Fallopian tubes, the acute infection usually subsides in eight to ten days and becomes subacute or chronic. The symptoms in a subacute or chronic tubal infection are extremely variable. Apart from the presence of a gonococcal infection elsewhere in the tract in association with pelvic inflammatory disease of the uterine adnexa which has followed on an acute attack, the diagnosis is difficult. Exacerbations of the condition during and after menstruation are common, and both dysmenorrhœa and menorrhagia occur as the result of chronic gonococcal infection of the tubes. In some of the less marked cases there may be few signs or symptoms present except those of general ill-health, neurasthenia, and a little pelvic cellulitis, which gives rise later on to the formation of fibrous tissue deposits in and around the tubes and ovaries.

Diagnosis.—In the acute stage it is often possible to demonstrate the gonococcus by staining methods or by culture in the discharge taken from the cervix subsequent to a menstrual period. Short of this the presence of a gonococcal focus elsewhere in the lower tract is strong presumptive evidence that the tubal condition is similar in origin. In the chronic stage it is more difficult to find the causal organism even subsequent to a menstrual period, and the diagnosis is dependent on the history of the case, the condition of the cervix, uterus, tubes, and ovaries, and the presence or absence elsewhere of the disease. The complement-fixation test and the cuti-reaction test may be employed as a diagnostic aid in chronic tubal and ovarian conditions, and are always positive if the infection is gonococcal.

In the diagnosis of all infections of the upper genital tract in the female, just as in cases of posterior urethritis in the male, the administration of one hundred to two hundred millions of polyvalent vaccine twenty-four hours prior to the taking of either bacteriological or blood specimens enhances the diagnostic value of the test, and enables one to discover a latent infection which has previously passed undiagnosed.

From the clinical standpoint the patient feels very ill, and in the acute stage the temperature is raised to 102° or 103° F. There is severe pain in the lower abdomen, and the pain is fairly sudden in its onset. In many cases the clinical picture simulates an acute attack of appendicitis, and in quite a number of cases where the tubal infection is most marked on the right side the appendix may be involved in the inflammatory process. Unless there is pus formation, neither vomiting nor boarding of the lower abdomen is so marked as in an acute appendix condition. The pain is more intermittent and

more of the nature of colic, and tends to radiate down towards the vulva and thighs. Bi-manual examination per vaginam will in most cases confirm or otherwise the presence of pelvic trouble. When the condition is acute the inflamed tube can be felt as a tender doughy mass on one or both sides of the uterus, and in some cases fluctuation can be detected. When the inflammatory reaction is less acute, examination per vaginam does not give such valuable information, and it is difficult to detect any definite enlargement of the appendages. The presence of adhesions in either fornix is suggestive, and recurrent acute attacks subsequent to each menstrual period are almost diagnostic. In virgins the examination may be made per rectum, when the cellulitic deposits or enlarged adnexa will be palpated.

In all cases of suspected infection of the tubes, ovaries, or pelvic peritoneum the careful weighing up of all the evidence, including the history, the presence of other genital or genito-urinary lesions, the menstrual history, and the history of previous abortions or pregnancies, must be considered in association with the clinical condition present. By doing so it is usually possible to come to an accurate diagnosis of the existing lesion.

Treatment.—In the acute stage absolute rest in bed is essential, the Fowler position being preferable. The lower bowel must be emptied by an enema, and an ice-bag or hot applications should be applied to the lower abdomen. Unless there is actual evidence of pus formation in the tubes and the patient is threatened with acute septic peritonitis, most cases will do better without operative interference. If relief cannot be obtained by the application of either heat or cold, and if the pulse rate increases while the temperature tends to drop and the patient looks ill, it may be essential to open the abdomen and get rid of the septic process. The greater number, however, of acute tubal conditions react well to rest, and as the acute condition subsides warm vaginal douches at a temperature of 110° to 112° F. assist in easing the pain and causing resolution of the inflammatory deposits. The heat of the antiseptic used is of more importance than its strength, but care must be taken that no force is used in administering the douche. Opiates should not be given either by mouth or per rectum until a definite diagnosis is arrived at. In cases in which operative interference is essential because of pus formation, the drainage should be free, and even if the acute condition is relieved by operative measures and the infected pus tube removed, it must be kept in mind that other parts of the genital tract are involved in the infective process, and treatment to eradicate this is essential. When the acute condition has subsided vaginal douching should be continued, and the patient should be given hot hip baths twice or thrice daily. In addition, tampons of glycerine and ichthyol 10 per cent may be inserted high up in the vagina and left in position for twelve hours at a time. The condition of the cervix should be attended to, and this or any other apparent lesion treated appropriately. When the symptoms have become less urgent the douche may be continued, but at less frequent intervals, and a vaginal tampon may be left *in situ* for thirty-six hours, douching being performed only after removal of the tampon and twelve hours later, prior to the insertion of the next one. Tonic aperients of iron, arsenic, and strychnine in combination with magnesium sulphate are valuable in this stage. The following preparation is especially valuable in out-patient work :—

R.	Magnesii sulph.	℥iss.
	Quin. sulph.	gr. xii.
	Liq. strychninæ	℥i.
	Tinct. ferri perchlor.	℥iiss.
	Glycerini	℥iss.
	Aquam menth. pip.	ad. ℥viii.
Sig.	One tablespoonful t. i. d. p.c. ex aq.					

In all types of inflammation of the uterine adnexa the administration of a detoxicated vaccine gives excellent results. In the acute stage a small dose only must be given, to

avoid setting up a gross general reaction. A patient suffering from acute salpingitis will tolerate, to begin with, a dose of 1000 millions of detoxicated gonococcal vaccine, and the dose may be gradually increased every fourth or fifth day if the initial reactions are not severe. In general the administration of vaccine lessens the severity of the infection, tends to prevent pus formation, and hastens the resolution of the inflammatory process. In subacute and chronic conditions the dosage may be appreciably increased, and in chronic cases doses up to 10,000 millions of detoxicated gonococcal vaccine are quite well tolerated. It is essential in these cases to examine repeatedly by culture the secretions from the cervix, and if necessary to prepare an autogenous vaccine of any superadded secondary infection so that it may be administered in combination with the gonococcal vaccine.

Of the alternative methods of treatment in acute tubal infections, the most favourable results have been obtained by the administration intravenously of electrargol $2\frac{1}{2}$ to 5 c.c. given daily while the symptoms are acute. Sulpharsenol also may be similarly used in doses of 12 to 24 centigrammes, and at times gives satisfactory results. Serum therapy, either specific or otherwise, has not given very consistent results.

CHAPTER XLIX

GONOCOCCAL INFECTION IN PREGNANCY AND IN THE PUERPERIUM

SYMPTOMS AND DIAGNOSIS ; TREATMENT

Gonorrhœal infection may be acquired prior to conception, at conception, or after it. If the infection is already present and the patient becomes pregnant, the disease, on account of the vascularity of the organs, is apt to extend more widely and to become more pronounced in its symptoms. When the infection is acquired at or immediately after conception it is also severe, and in the large majority of cases extends throughout the whole urogenital tract.

Symptoms and Diagnosis.—The clinical picture varies according to the part most affected. The symptoms present are always severe, and resemble very closely those seen in the non-gravid state subsequent to a menstrual period. The gonococcus is more easily demonstrable in the discharges from the urethra, cervix, and vagina during pregnancy than at other times, and the increased swelling, vascularity, and moisture of the parts induce the formation of condylomata acuminata, which are very difficult to get rid of during pregnancy. Metastatic complications are common in connection with pregnancy.

In the puerperium an infection which has been previously latent for months may flare up and give rise to very acute symptoms simulating a puerperal sapræmia or septicæmia. It is difficult to distinguish puerperal sepsis due to the gonococcus from that due to other micro-organisms from the clinical standpoint, but bacteriological examination of the discharges from the cervix will very frequently demonstrate the causal organism, and culture on a special medium is more certain evidence still. In cases of puerperal sepsis solely due to the gonococcus the febrile attack is said to occur later ; but so frequently are other micro-organisms, such as the staphylococcus and the streptococcus, present as contributing factors to the infection, that, apart from bacteriological evidence, it is impossible to differentiate them unless there is a history of gonococcal infection prior to labour.

Treatment.—The treatment of the puerperal condition is essentially the clearing up of the infection prior to the onset of labour. All the methods mentioned in the foregoing chapters in the treatment of the various parts affected should be carried out, but great care must be exercised in the examination of the patient, in the taking of specimens, and in the application of local treatment. Douching is not advisable at any stage of pregnancy, and local applications to the cervix or the inserting of plugs into the fornices are contra-indicated, because of the risk of inducing abortion. Warty growths should be kept as clean as possible by swabbing and subsequently dressing with a dusting powder to keep the opposing surfaces dry. Treatment of the urinary tract and of the lower genital tract is admissible in the same way as in the non-gravid state, but the greatest care must be taken that the infection is not spread upwards. From the fact that local treatment is so limited both during pregnancy and in the puerperium, the best results are obtained in both conditions by vaccine therapy. There is no doubt that the increased vascularity of the parts tends to make the infected areas more easily accessible to the

circulating antibody, and the keeping of the parts clean locally is in many cases all that is required in addition to the administration of a polyvalent detoxicated vaccine. The same treatment is applicable in the puerperium, but at this stage both vaginal and intra-uterine douching help to reduce the fœtor and to get rid of the septic products of infection by establishing efficient drainage.

In all cases both before and after labour it is essential to watch the patient over a prolonged period to make certain that all foci of infection have been cleared up.

CHAPTER I

THE URETHROSCOPE

GENERAL RULES FOR USE—INDICATIONS FOR USE IN DIAGNOSIS AND TREATMENT—PREPARATION OF PATIENT—VARIETIES OF MODERN INSTRUMENTS—TECHNIQUE OF POSTERIOR URETHROSCOPY—NORMAL APPEARANCE OF URETHRA—PATHOLOGICAL CONDITIONS OF URETHRA—ACUTE CONDITIONS ; PERI-URETHRAL ABSCESS—MEATAL OR INTRA-URETHRAL CHANCRE—SUBACUTE CONDITIONS ; SINGLE OR MULTIPLE LITTRITIS—CHRONIC CONDITIONS ; GRANULAR CONDITIONS OF URETHRA—POLYPI OR WARTY GROWTHS—POSTERIOR URETHRA—URETHROSCOPE IN TREATMENT OF CHRONIC STRICTURE

THE urethroscope has been referred to in the preceding chapters on subacute and chronic urethritis. In complications—such as infiltration and stricture—which follow on many cases of urethritis, this instrument is of value in diagnosis, prognosis, treatment, and observation of the effect of treatment. While the use of the instrument is largely confined to cases of urethritis in the male, it also has its place in the treatment of female urethritis and can be utilised to examine the cervix and vagina in cases of vulvo-vaginitis in children. It is essential to observe all the rules of asepsis which apply to general surgery in this as in all forms of treatment of the mucous surface of the urinary tract. The operator's hands, the parts surrounding the meatal orifice, and especially the glans and prepuce, must be thoroughly cleansed ; sterile towels are applied round the exposed genitals, or a sterile square of lint with a central aperture through which the penile organ can be handled may be used. The urethroscope itself requires special care in sterilisation, as certain parts, such as the optical apparatus, cannot be boiled. All such parts are carefully cleansed before and after use with methylated spirit or with a solution of 1/2000 biniodide of mercury. When not in use such parts should be kept in an air-tight cabinet rendered sterile by formalin vapour. Of the parts which may be sterilised special attention should be paid to all angles and crevices of the instrument, and especially to the inner surface of the urethroscopic tube.

General Rules for the Use of the Instrument.—With very few exceptions this instrument should not be used during the acute stage of urethritis or of any of its complications. The urine passed in the first test glass should, if possible, be free from turbidity in subacute and in chronic conditions before utilising the instrument for diagnostic purposes. When an accurate picture of the condition of the mucous surface and of the openings of the gland ducts is required, it is advisable that the patient should not urinate for at least two to three hours prior to the examination. This also applies to cases in which it is desirable to observe the effect of treatment. When, on the other hand, operative measures or the local application of an antiseptic or other therapy are undertaken through the lumen of the urethroscopic tube, it is always desirable, before passing the instrument, that the patient should pass water and, in addition, that the whole of the urethral tract should previously be washed out with a mild antiseptic.

Indications for the Use of the Urethroscope : (*a*) *In Diagnosis.*—During the sub-

acute stage of urethritis it enables one to locate the position of an infected gland duct and to estimate whether the littritis is generalised or confined to one or two of Littré's gland ducts. In the chronic stages of urethritis and in conditions giving rise to a morning gleet it enables one to see accurately the condition of the mucous surface and to judge whether the mucoid discharge or the gleet is the result of chronic infiltration in and around the lacunæ and gland ducts, or of gross stricture, or of a general granular condition of the mucous surface. Similarly, in cases of urethral discharge not necessarily gonococcal in nature, it enables one to locate a polypus or a patch of leucoplakia. In stricture it enables one to locate the site of the stricture, its nature, its dilatability, and its extent, and is extremely valuable in differentiating stricture from spasm and from a congenital diverticulum.

(b) *In Treatment.*—Accurate diagnosis at once suggests the appropriate treatment and the amount of treatment required in any case; in a case, for example, of soft infiltration of the anterior urethra, dilatation by means of a Kollmann's dilator is indicated. In a case of stricture, where it is impossible to pass even a filiform bougie, urethroscopic examination will accurately locate the stricture, and under air inflation a filiform bougie may be passed into the stenosed aperture under the guidance of the eye. It was previously mentioned that the instrument was rarely required during the acute stages of the disease. A peri-urethral abscess, however, in the early stages can be most effectively dealt with by incising it through the urethroscopic tube. This method avoids many complications and establishes drainage more quickly than any other method. The instrument may also be used in the acute stages to enable one to obtain a specimen for dark-ground illumination in suspected cases of intra-urethral chancre. Local antiseptic therapy, or electro-therapy through the lumen of the tube, has a limited use only, because in the greater majority of cases the infection of the gland ducts is a generalised one and not confined to one duct only. In addition, it is difficult to be certain that any cautery or antiseptic locally applied will penetrate along the ducts of Littré to the depth of the gland and not invaginate only a part of the infected structure.

Preparation of the Patient for Urethroscopic Examination.—In the acute stage the urethra is washed out before passing the instrument. In subacute and chronic cases, where it is essential to see the unaltered mucous surface, the patient is examined at a time when he has retained urine for three to four hours. In cases of known stricture it is always advisable to wash out the urethra before passing the urethroscope, and if this plan is adopted in this and in other instrumental work on the urethral tract the so-called catheter fever will seldom be met with. During the operation the patient should be at all times in the recumbent position. If the meatal orifice is narrow it may be necessary, as a preliminary to urethroscopic examination, to dilate the orifice with solid sounds or to perform meotomy and postpone the examination of the mucous surface to three or four days later.

Varieties of Modern Instruments.—While many designs of instrument are now available, all of them consist essentially of a hollow metal tube with an obturator. In the anterior urethroscope the tube is straight. Magnifying lenses of correct focal length are attached to the distal end of the tube and assist in giving a magnified and more detailed view of the field. The illuminating apparatus is supplied by an electric lamp attached to a dry battery or pantostat. In such instruments as have internal illumination the lamp is carried on a long thin stem to the lower proximal end of the tube. Examples of this type of urethroscope are those invented by Luys, Woolf, Cambell, or the Holborn Surgical Company. External illumination is employed in the Wyndham Powell and Swift Joly instruments. The light in these latter is reflected down the tube by mirrors focussed accurately by means of an adjustable bull's-eye lens. In many of the instruments, such as Cambell's, the Holborn, Wyndham Powell, and the Swift Joly, there can be and is attached to the outer part of the urethroscopic tube an observation chamber by means of which air may be introduced into the urethra through a lateral opening and the parts can be examined under air distension. This latter attachment is of great assistance in

operative work inside the urethral canal. The type of instrument with internal illumination is perhaps the easier to manipulate for the beginner, although the instrument with external illuminating apparatus and that for air dilatation will enable one to cover a wider field of work.

For examination of the posterior urethra internal illumination is essential and is employed in the Woolf, Luys, Wossidlo, and Buerger apparatus. The tube in these latter instruments has a slight prostatic curve. It is advisable in all instruments for the examination of the posterior urethra to have an arrangement attached for water cooling. In gonococcal infection, however, posterior urethroscopy is only required in exceptional cases, such as those of recurrent epididymitis and of suspected polypi. Prior to its use it is always advisable to anæsthetise the urethra. Rarely is local anæsthesia required with the anterior instrument.

Method of Use and Technique.—Having prepared the patient as previously indicated, sterilised the instrument, and placed the patient in the recumbent position, the operator takes his place either on the right side of the patient or, if the patient is in the lithotomy position, between the patient's thighs. Subsequent to cleansing the penis and meatal orifice, a sterile square of lint with an aperture in its centre is placed over the pelvis and the penis is drawn through it. The operator holds the penis with the left hand, and after lubricating the urethroscopic tube, with obturator still in position, with sterile catheter lubricant, the instrument is gently passed into the meatus and along the urethral tract. The instrument should not require to be forced along, and in many cases will pass by its own weight into the canal. Having passed the instrument, the obturator is withdrawn, and the lumen of the urethra is cleansed of lubricant and excess of moisture by sterile cotton-wool swabs mounted on a long probe. The lighting circuit is then tested, and is inserted into the tube in the case of instruments with internal illumination; in those with external illumination the light is attached to the battery and the mirrors are properly focussed. Subsequent to this the bulb for air inflation is attached. If the eye of the examiner is now applied to the magnifying lens, the instrument may be manipulated until the lumen of the canal is central and the longitudinal folds of the mucous surface are seen to radiate from a central figure in regular striations. By gradually withdrawing the urethroscopic tube along the canal, the operator is thus enabled to observe any alteration in structure and any abnormalities or pathological conditions present in the membranous, bulbous, or penile urethra and to locate their exact position.

The Technique of Posterior Urethroscopy.—The technique of posterior urethroscopy is more difficult. The patient is prepared in a similar manner, but before inserting the instrument a small quantity of 2 per cent novocain or 2 per cent alypin is instilled into the deep urethra. The curved posterior urethroscope, well lubricated, is passed as far as the bulb, the point is elevated towards the pubic arch and gradually insinuated slightly further into the canal, the outer end of the instrument is depressed to rotate the point of the instrument under the arch of the pubis, and with a little gentle pressure it is carried into the vesical sphincter. If there is any difficulty in inserting the instrument the forefinger of an assistant inserted into the rectum enables one to slide the instrument along the finger and to guide it into the neck of the bladder. The obturator is then withdrawn, and if urine oozes out of the tube the instrument is slightly withdrawn and the excess of urine mopped up with swabs mounted on a probe; the water-inflation apparatus is now attached, and finally the lighting attachment.

Normal Appearance of the Urethra.—No amount of study of urethroscopic paintings will convey to the beginner a true idea of the appearance of the lining membrane of the urethra. Only by continuous practice in examining patients with a normal urethral tract will the student become proficient in noting any pathological changes in the lining membrane or in the openings which branch off from it. The colour of the urethra varies at different parts from a pale pink to red, and the colour is deeper red the further back it is seen. It is smooth and glistening and shows its longitudinal folds radiating in circular

fashion from the central lumen ; the blood-vessels appear as red or faint pink striations running in a longitudinal direction. The glandular portion of the urethra is the only part in which the striations are not marked, and the mucous membrane lining it is of firmer consistence and lacks the dilatibility of other parts of the urethra. About 2 to 3 cm. from the meatus, situated on the roof, is the lacuna magna, the free edge of which is known as the valve of Guérin ; in association with this lacuna there is a gland which opens into its base. The central lumen in this part of the urethra appears as a vertical slit ; further back in the penile or pre-bulbar part of the anterior urethra the central opening is circular, and further back still in the bulb it is ovoid, and may at times be transverse. In the pre-bulbar portion the mucous membrane presents a pinkish red colour, and the openings of the gland ducts of Littre and the lacunæ of Morgagni are apparent on the roof and lateral walls. The lacuna are in the nature of small depressions of varying depths, and at times they appear like a small valve, the base of the valve being directed to the meatal orifice. They are more numerous in the anterior portion of the penile urethra and lessen in number towards the bulbar part. The openings of the gland ducts of Littre are in a normal urethra scarcely visible, but under air distension they may be seen as small pin-point depressions on the dorsal and lateral walls of the urethra ; occasionally they occur on the floor of the urethra, but are not so numerous in this situation. They increase in number from the glandular portion backwards to the bulb, but rapidly decrease in number when the membranous urethra is reached. Frequently a Littre's gland may open into the floor of one of the lacunæ. In the bulbous urethra the mucous membrane is rather deeper in colour than in the penile portion. The floor of the bulb shows a number of folds of mucous membrane which conceal the openings of Cowper's gland ducts ; under air distension these openings are apparent, one usually being slightly anterior to the other. The roof of the bulb has a considerable number of folds which, apart from air distension, mask the openings of Littre's gland ducts. In the membranous portion of the urethra the action of the compressor urethræ muscle throws the membrane into regular folds, and there are few, if any, gland structures present in this part of the urethra. The posterior urethra is deep red in colour and generally very vascular, but may appear less vascular, due to the action of the anæsthetic and of the irrigating fluid which is used during the examination. The verumontanum comes into view and projects into the lumen of the urethroscope as a raised ridge on the floor ; in the centre of it there is a small depression known as the utricle, and on either side, at the base of the ridge, a groove known as the prostatic sinus with five or six small openings into it. These openings are not unlike the openings of Littre's gland ducts in the anterior urethra, and are the mouths of the prostatic ducts. In the same situation, at the base of the verumontanum, there may be seen a somewhat larger opening one on either side, but nearer to its apex than the openings of the prostatic ducts. These larger openings are the ejaculatory ducts of the seminal vesicles. The verumontanum gradually inclines towards the vesical sphincter, which is seen as a deep red ring, and beyond this there is a paler yellow mucous membrane of the bladder.

Pathological Conditions of the Urethra.—The conditions which can be diagnosed by the urethroscope may be divided into acute, subacute, and chronic lesions. Among the former may be included peri-urethral abscess, meatal and intra-urethral chancre. Among the subacute lesions may be mentioned littritis, localised or general, cowperitis, and early soft infiltration. Among the more chronic lesions may be mentioned transitional and hard infiltration or stricture, chronic littritis, granular conditions of the urethra, warty growths, papillomata, and patches of leucoplakia.

Acute Conditions: *Peri-urethral Abscess.*—Before examining by the urethroscope in this condition it is advisable to wash out the urethra gently with mild warm antiseptic. The tube with the obturator *in situ* is then passed with extreme care. The tube, on touching the bulging wall, is insinuated gently past it, and, after withdrawing the obturator and attaching the lighting mechanism, the lumen of the urethra is examined. As the

tube is gently withdrawn the mucous membrane is seen to be hyperæmic, and small bleeding points appear all over the tender surface. As the area of the abscess comes into view in the lumen of the urethroscope it bulges into it, and in some cases, if the abscess is extensive, it may fill up the whole lumen. Before incising with a urethrosopic knife through the lumen of the tube it is always advisable to apply 2 to 4 per cent novocain with a little adrenalin added to it. This lessens the amount of bleeding and subsequent spasm which may give rise to trouble after incision. The progress of the condition towards subsequent cure may be observed by examinations repeated at a later date.

Meatal or Intra-urethral Chancre.—When examined through the urethroscope an intra-urethral chancre appears as an erosion with slightly raised edges. The common situation is the lacuna magna, and through the urethroscope the surface of the ulcer may be gently curetted and a specimen taken for dark-ground illumination or staining.

Subacute Conditions: *Single or Multiple Littritis.*—In littritis with associated soft infiltration—two conditions which are often associated—the mucous membrane is swollen, red, and angry, and appears cedematous though still retaining its lustre. If the patient is examined at a time when he has retained urine for three to four hours, small beads of pus may be seen oozing from one or more of Littré's gland ducts. The striations are masked by the accompanying oedema and vascularity, but the urethra is still dilatable. There is always, on examination of this condition, a tendency to slight oozing of blood unless great care is exercised in the manipulation of the urethroscope.

A similar condition is seen in association with cowperitis, and on air inflation of the bulb the orifices of Cowper's ducts stand out quite prominently. There is usually considerable reddening around the orifices, and a small bead of muco-pus may exude from one or other of them during the examination.

Chronic Conditions.—Transitional or hard infiltration and chronic littritis arise from untreated or partially treated acute conditions. The oedema and vascularity of the urethra gradually disappear, and in its place there is increased formation of submucous fibrous tissue. The striations of the urethra become irregular or disappear and the mucous membrane loses its dilatability. The surface is often of a dull unhealthy grey appearance, with streaks of muco-pus or mucus only appearing in and around the openings of the gland ducts. If untreated the condition becomes progressively more indurated and fibrous, and the fibrosis is more marked in and around the openings of the gland ducts. This quiescent increase of fibrous tissue in course of time leads to gross hard infiltration or stricture; the mucous membrane loses completely its dilatability and becomes progressively less vascular.

Granular Conditions of the Urethra.—In certain cases of chronic urethritis with gleet the whole mucous surface appears granular and unhealthy without any apparent localised infiltration. The striæ are irregular and the gland ducts appear pouting and exude a mucous secretion. Such a condition is often the result of over-treatment, and especially treatment with too strong antiseptics. Treatment through the urethroscope is of little value, but is essential for observation of the effect of mechanical dilators on the condition.

Polypi or Warty Growths.—Polypi, small warts, and patches of leucoplakia have the characteristic appearance through the urethroscope which they have on any other mucous surface. The curette or the electric cautery may be passed along the lumen of the urethroscope to remove either of the two former conditions; the latter condition is best left alone, as it is usually the result of over-treatment and irritation.

Posterior Urethra.—In the posterior urethra polypi may give rise to considerable trouble. They may occur either as flat warty growths, or they may be pedunculated. They are usually pale and translucent and resemble granulomata. After passing the posterior urethroscope they can be removed by either the electric cautery or the curette under local anæsthesia.

The Urethroscope in the Treatment of Chronic Stricture.—In cases of old-standing urethritis, where a hard infiltration has persisted for years until an established stricture

has been formed, the urethroscope has revolutionised and put on a scientific basis the treatment of such stricture. It enables the operator to locate the opening of a stricture without needless damage to the surface of the urethra proximal to it, and, under air inflation and accurate observation, to pass into the opening of the stricture a filiform bougie. To facilitate this there is supplied a special eye-piece with a urethroscope of the type of Cambell's and other air-inflation instruments. In such cases local anæsthetic may be applied to the face of the stricture prior to the passing of the instrument with a view to overcoming the associated spasm. When the filiform bougie has been inserted through stricture it should in all such cases be tied in for twenty-four hours and the patient's urine allowed to dribble along the side of it. On removing the filiform bougie twenty-four hours later it is almost always possible to pass an instrument two or three sizes larger without much difficulty. This is a method which is more suitable than any other in dealing with extensive stricture formation, and if carefully carried out will appreciably lessen the number of cases in which internal urethrotomy is called for.

CHAPTER LI

GENERAL MANAGEMENT OF THE PATIENT AND THE STANDARD OF CURE IN GONORRHŒA

MENTAL FACTOR IN GONORRHŒAL PATIENT—STANDARD OF CURE IN GONORRHŒA

The Mental Factor in Gonococcal Infection.—In all stages of the infection it is essential to guard against sexual neurasthenia in both male and female patients.

The patients at their first visit are always anxious to know if they have the disease and whether they can be cured of it. A definite answer should be given in every case after careful examination. Combined clinical and bacteriological examination enable one to give an accurate diagnosis of whether the condition is gonorrhœa or not, and it is always inadvisable to tell a male patient that he is only suffering from some slight strain, or a female patient that she has a chill, with subsequent leucorrhœa. The seriousness of the condition should not be over-emphasised, but at the same time the importance of getting completely cured of it and of being under observation for a considerable time should be brought home to the patient. The more definite one is in diagnosis the more likely is the patient to be impressed with the importance of carrying out rigidly all instructions regarding treatment. When a patient expresses anxiety regarding certainty of cure one can assure every patient that gonorrhœa is a curable disease, even if at times the cure is slow and tedious. The common form which introspection takes in patients suffering from gonorrhœa is the habit of carefully watching at each examination what the surgeon does. The examination of the urine, the examination of the discharge, the results of prostatic massage, and all other details of treatment impress themselves on a patient's mind, and he in turn is apt to be constantly performing the same examination and looking for threads in his urine from day to day. This should be discouraged, and can be avoided by telling the patient from time to time how he is progressing and by giving him as optimistic reports as are justified by the clinical and pathological findings. Absolute obedience to all instructions with regard to food, drink, and absence from all physical and mental exertion plays a great part in the treatment and cure. In no group of diseases does the personality of the medical attendant and confidence in him weigh so largely as in venereal disease. Meticulous care in all the little details of treatment counts for a great deal, and if this attitude of mind is obtained in the patient, and complete confidence established, there will in most cases be little difficulty in getting him to continue under observation and treatment until he can be safely assured that his condition is completely cured. The surgeon who trusts to clinical signs only, and even more so he who trusts to the reports of a patient only, without using the microscope and the urethroscope, cannot possibly assure his patient of cure. It is failure to use these and other all-important methods of diagnosis and treatment that is responsible for the many uncured cases of latent gonorrhœa which result in so many disastrous marriages and countless suffering. Prolonged observation after apparent clinical cure is as essential in gonorrhœa as in syphilis, and the test of time is valuable in supplementing other scientific methods in establishing a cure.

Standard of Cure in Gonorrhœa.—It is difficult to lay down an absolute standard in a case of male infection, and still more so in a female case. In both, however, certain requirements are essential, and the attainment of these must be within the reach of any competent medical practitioner, and must not be so irksome and tedious that the average patient will not tolerate them.

In the male sex the following conditions are essential for a cure :

1. Absence of any sign of urethral discharge and absence of pus cells from the morning urine for a period of at least fourteen days after treatment has been suspended.
2. Absence of gonococci in films of either urethral or prostatic discharge. These films should be taken on two separate occasions subsequent to the disappearance of clinical symptoms.
3. Absence of any clinical or bacteriological signs of disease subsequent to the administration of a provocative injection of 200 millions of polyvalent gonococcal vaccine. The specimens for bacteriological examination are taken at intervals of twenty-four to forty-eight hours subsequent to the administration of the vaccine.
4. Urethroscopic examination of the mucous membrane of the urethra, to ensure that it is not damaged or infiltrated and that it has regained its lustre and retained its dilatability.

If at any of these examinations any abnormal condition is found, it may be essential for assurance of cure to employ other methods, such as suction and dilatation of the urethra, and the test examination is again repeated when these four primary requirements have been attained. When these preliminary tests have been passed, the patient may be given a provisional assurance that his condition is nearing cure. One or two months' rest from all treatment may now be given, and the clinical, bacteriological and urethroscopic tests, or in addition a cultural test, be repeated when he reports again. If these latter tests prove satisfactory, the patient should be instructed to resume his ordinary habits of life, even to the taking of alcohol in moderate quantities, and should report again for examination six months subsequent to the first or apparent clinical cure. If no sign or symptom of disease has been apparent during this probationary period of four to six months after cessation of actual treatment, serological examination of the blood by the complement-fixation test may be performed, and, if negative, will help to establish the certainty and permanency of the previous findings. Prior to such complement-fixation test a provocative injection of gonococcal vaccine is of value in intensifying or indicating the absence or otherwise of a latent infection. During the four to six months when the patient is under observation he should be encouraged and told definitely that the aim is to give him a certainty of cure as opposed to an apparent cure. He should be discouraged from examining himself, and told that once a cure is attained he may resume his place in society without any fear or risk of recurrence of the condition if he conforms to the ordinary rules of civilised life.

In the female the method of testing for cure, although more difficult, proceeds along the same lines. The essentials are :

1. Absence of all clinical symptoms of disease for one month after cessation of treatment.
2. Absence of all evidence of disease on bacteriological and cultural examination of the discharges from the urethra, cervix and Bartholinian ducts. The specimens for such examinations should be taken subsequent to two successive menstrual periods after apparent clinical cure, and it is an additional safeguard and makes the test a more potent one if, twenty-four hours prior to the taking of the specimens, a glycerine plug is inserted into the cervix and 200 millions of polyvalent gonococcal vaccine is administered simultaneously as a provocative injection.

3. Urethroscopic examination, to ensure the absence of any involvement of Skene's ducts and the absence of infiltration of the urethra.
4. Bi-manual examination of the pelvic contents, to ensure that there is no gross pelvic peritonitis or other lesion.

When this has been attained the female may be provisionally considered free from infection, but the tests should be repeated once during the ensuing three months, and especially so within twenty-four to forty-eight hours after the cessation of a menstrual period. When six months have elapsed from the cessation of active treatment and apparent clinical cure, the complement-fixation test of the blood for gonorrhœa should be carried out as in the case of male patients. The tests are made more searching by giving prior to them a provocative dose of gonococcal vaccine. When a patient has fulfilled all these conditions and passed these clinical, bacteriological and serological tests, she may be considered completely free from her infection.

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